JOHN E. FOGARTY
INTERNATIONAL
CENTER
FOR ADVANCED
STUDY IN THE
HEALTH SCIENCES

National Institutes of Health Annual Report of International Activities

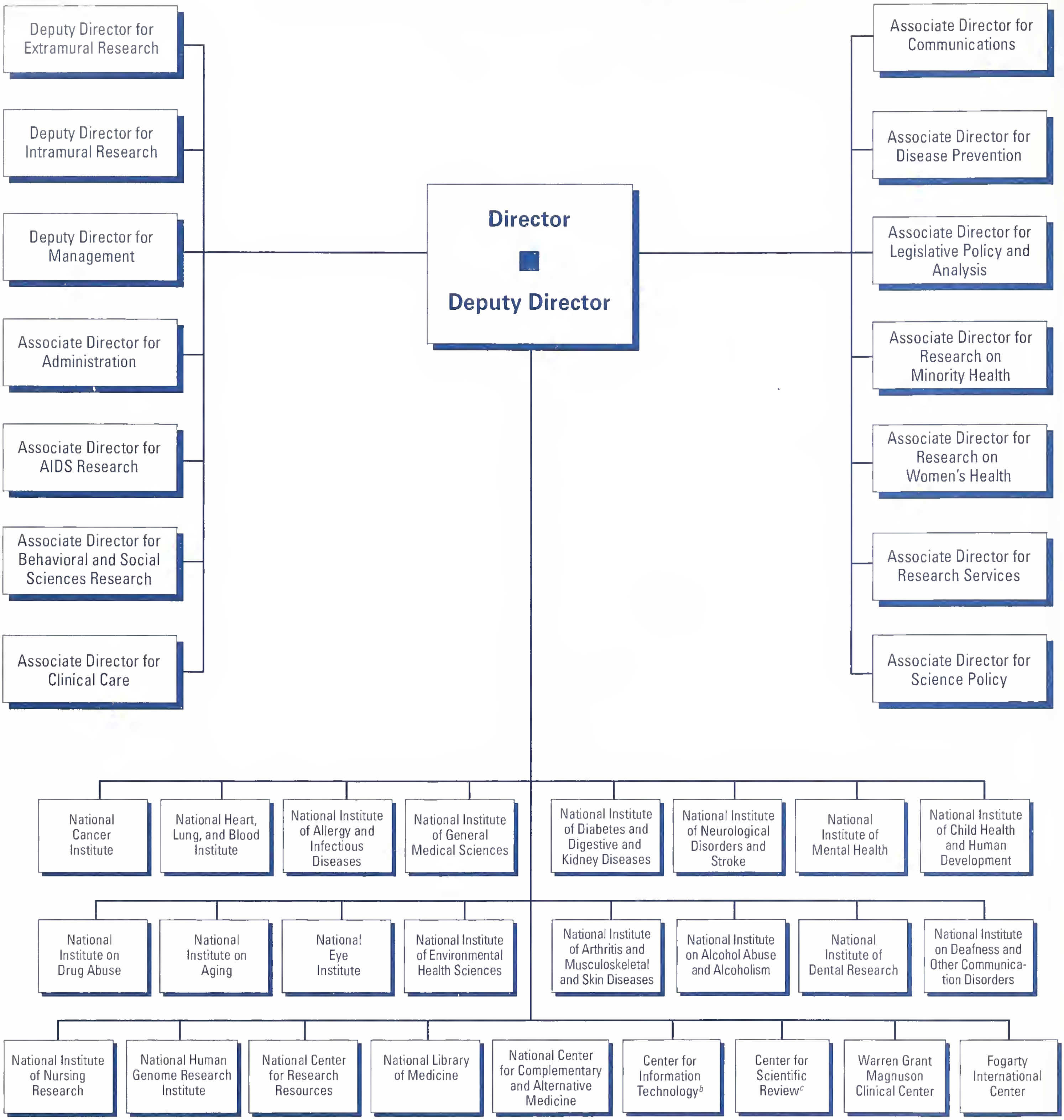
Fiscal Year 1998

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

Public Health Service

National Institutes of Health

National Institutes of Health[a]



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- National Institute of Child Health and Human Development
- National Institute on Drug Abuse
- National Institute on Aging
- National Eye Institute
- National Institute of Environmental Health Sciences
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Institute on Alcohol Abuse and Alcoholism
- National Institute of Dental Research
- National Institute on Deafness and Other Communication Disorders
- National Institute of Nursing Research
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- National Library of Medicine
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- Center for Scientific Review[c]
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[a] Use of funds for printing this periodical has been approved by the Office of Management and Budget.

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I.

Overview of International Activities

HISTORICAL PERSPECTIVE

The National Institutes of Health (NIH) has been linked with the international scientific community since its founding in 1887 as the Laboratory of Hygiene. A principal reason for Congress' establishment of this precursor for the NIH was to combat diseases that were international in scope and threatened the health of U.S. citizens. Shortly before his appointment as the first Director of the Laboratory of Hygiene, Dr. Joseph Kinyoun traveled to Europe to learn new techniques for isolation and identification of bacteria in the laboratories of Robert Koch and Louis Pasteur. Returning to the United States, he proceeded to isolate the cholera microbe from sick crew members of a ship in the port of New York City. These efforts stemmed the importation of the sixth cholera pandemic into the United States, in the first use of the new science of microbiology to address a public health problem.

Ever since the early microbial investigations of Dr. Kinyoun, the NIH has continued a tradition of international research. The components of the NIH with an international program have expanded as the NIH's legislative mandate has broadened. NIH international activities were codified in the International Health Research Act of 1960, which authorized the Public Health Service to provide grants and fellowships to foreign institutions and to facilitate the international exchange of research scientists.

Subsequently, the NIH investment in international activities has grown in direct proportion to the overall budget, representing a level of about 1.5%–2% of NIH expenditures over the past two decades. In absolute terms, this represents the largest investment by any U.S. Government science agency in international biomedical research cooperation and reflects an implicit and historical working principle of the NIH—that neither disease nor intellectual pursuit can be confined within national boundaries.

NEW CHALLENGES

With the growing application of biological progress and new technologies to the solution of practical clinical problems, promising advances are possible in the diagnosis, treatment, and prevention of disease. Increasingly, the capacity to capitalize on scientific opportunities and capture the potential of discoveries will depend on scientific interaction on a global scale among biomedical, epidemiologic, and behavioral researchers in the field and in laboratories, together with clinical and technical personnel in all areas of science. The growing interdependence of the world's scientific community is attributable to recent promising developments that present new challenges and opportunities.

EMERGING TECHNOLOGIES

International cooperation enables the U.S. scientific community to share unique or highly sophisticated research methods, technologies, and facilities located abroad. This access grows increasingly important as the biomedical and behavioral sciences become more specialized and at a time when only a cluster of laboratories may be undertaking a specific line of scientific inquiry in molecular genetics, developmental and structural biology, neurobiology, or other highly specialized fields.

The convergence of parallel lines of research through international interaction provides for cross-disciplinary approaches that often catalyze new discoveries. The development of a therapeutic agent, for example, may result from exchange of concepts and methods enabling investigators in one laboratory to determine the amino acid sequence of an important enzyme, researchers in a second to crystallize and define its three-dimensional structure, and scientists in a third to exploit these basic research findings to design a novel drug-delivery system.

POPULATION-BASED STUDIES

The availability of unique populations and environments in other regions of the world presents important opportunities to expand the biomedical knowledge base and conduct studies that could not be undertaken in any one nation. Advances in technologies for analysis of DNA have accelerated the rate of drug and vaccine development and hold promise for new and improved approaches to prevention and treatment. Many of these emerging medical technologies will require studies in regions of the world where there is a high concentration of particular diseases.

A notable example is the development of an effective vaccine for acquired immunodeficiency syndrome (AIDS). This achievement will depend on testing in various countries, because of genetic variability of the virus and increasing incidence of human immunodeficiency virus (HIV) in important cohorts. Other prominent examples of benefit from international field trials include the development of new and improved treatments and preventive measures for diarrheal, respiratory, sexually transmitted, and parasitic diseases; hepatoma and other virus-associated cancers; and cardiovascular diseases.

Future advances to identify genetic markers for inherited diseases and predisposing factors for acquired diseases will require genetic-linkage studies that transcend national borders. Past international cooperation has made possible the identification of genetic markers for thalassemic syndromes, Huntington's chorea, cystic fibrosis, and a hereditary form of colon cancer. This progress was possible through the study of inheritance patterns among populations of countries with a high prevalence of the inherited disease, which enabled scientists to localize and ultimately isolate the disease-related gene.

Population-based research involving cross-cultural comparisons provides new knowl-

TABLE I-1.

International Agreements Involving the NIH, Fiscal Year 1998

Country/Area	Science and Technology	Health	NIH	No. of Agreements
Argentina	1972			1
Armenia	1997		1995 NIH-MOH-AOS	2
Australia			1974 NLM	1
Austria			1993 NIH–FWF	1
Brazil	1994			1
Canada	1997		1982 NLM–CIST	2
Chile	Pending		1997 NIH–CONICYT	1 (1 pending)
China	1991	1998	1987 NEI–ZOC 1996 NLM-CUHK	4
Croatia	1994			1
Czech Republic	1991			1
Egypt	1995	1989		2
Estonia	1994			1
Finland	1992	1982		2
France			1974 NIH–INSERM	1
Germany	1994	1998	1981 NCI–MORT 1983 NLM-DIMDI	4
Hungary	1989		1981 NCI–NIO	2
India			1987 NLM–NIC	1
Israel	1972	1985	1983 NIH–HU 1993 NLM–HU	4
Italy	1993	1981	1978 NLM–ISS 1985 NEI–MOH	4
Japan	1993	1965	1974 NCI–JSPS 1974 NLM–JIST 1976 NEI–JSPS	5
Korea	Pending		1989 NCI–KAMS 1991 NLM–SNU	2 (1 pending)
Kuwait			1981 NLM–MPH	1
Latvia	1994			1
Lithuania	1994			1
Macedonia	1995			1
Mexico	1994	1996	1976 NLM–MOH 1994 NIH-CONACYT	4
New Zealand	1991		1991 NLM–DOH	2
Poland	1997			1
Russia	1993	1994	1987 NEI–IED 1994 NIH–RAS 1997 NLM-SCSML	5
Slovakia	1996			1
Slovenia	Pending			1 (pending)
South Africa	1995		1976 NLM–MRC	2
Spain	1994			1
Sweden			1974 NLM–SMRC	1
Switzerland			1980 NLM–SAMS	1
Turkey	1994			1
Ukraine	1994			1
United Kingdom	1995		1974 NLM–BL	2
Venezuela	1996	1996		2
Taiwan			1987 NLM–EPA 1989 NIH-NSCT	2
Total: 40	**29 (3 pending)**	**10**	**34**	**72 (3 pending)**

edge of the natural history, epidemiology, and risk factors associated with diseases of public health priority. These studies use geographic differences to discover and differentiate genetic and environmental determinants of disease. Correlations between sodium intake and stroke, for example, were identified and confirmed through international studies. Cross-national investigations also provide for a greater degree of international acceptability of results.

EMERGING DISEASES

The spread of infectious diseases across national borders and the emergence of new pathogens dramatize the need for international cooperation in health research. The rapidity with which the AIDS virus was transmitted among continents highlights the necessity for an effective global sentinel network of basic and clinical researchers to identify new patterns of disease and modes of transmission. Although the AIDS epidemic has exhibited the difficulties of coping with a new infectious disease, AIDS is but one of a dozen new or newly recognized viral diseases that have emerged in recent decades in association with rapid social and ecological change.

RESOURCE SHARING

International cooperation enables the United States and other countries to share the cost and labor of scientific discovery. Leading examples are the initiative to map and measure the sequence of 3 billion nucleotide base pairs in the human genome; efforts to analyze plant, animal, and microbial model organisms; and multicenter, standardized studies requiring the recruitment of an extensive study population.

Opportunities to share important resources are also presented through international cooperation. Collaborating investigators in other countries have provided more than one-half of all compounds that have been screened for antineoplastic or antiviral activity at the NIH. GenBank, a computerized source of information on genetic sequence, was developed in concert with the European Molecular Biology Laboratory. Sharing of genetically modified rabbit models developed in Japan provided observations that led to the discovery of the role of critical receptors in the atherosclerotic process.

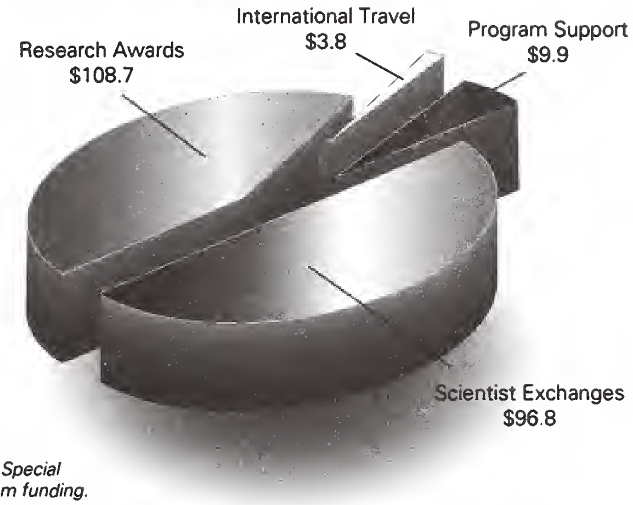
Other examples of the benefits of international cooperation include

- highly specialized treatments for rare or uncommon hereditary and acquired disorders, when no one country can recruit an adequate number of patients for meaningful study;
- the shared use of sophisticated and costly instruments that are beyond the effective resources of any one institution, such as particle accelerators to study macromolecular structures;
- foreign registries for cancer and other diseases that have supplemented population studies in the United States; and
- international repositories for standardized chemicals, cloned genes, viruses, and antisera, as well as international donor registries for bone marrow.

INTERNATIONAL RELATIONS

The international role of the NIH is expanding as a result of what has been characterized as a changing world order. Global political and economic realignments have immediate relevance to a Federal science agency with an international mission and to universities that have forged international relationships. These global changes include the collapse of communism and the emergence of new democracies, European economic integration, the economic ascendance of Japan and neighboring Pacific Rim nations, and widening disparities in health and economic status between industrial and developing nations.

FIGURE I-1.
NIH International Activities Funding by Mechanism, Fiscal Year 1998[a] (in millions of dollars)



[a] *Excludes $1.3 million of Special Foreign Currency Program funding.*

HIGHLIGHTS OF RECENT INTERNATIONAL SCIENTIFIC ACTIVITIES

This report discusses the international activities of NIH components: work undertaken intramurally, by staff or visiting foreign scientists, and extramurally, by NIH grantees collaborating with foreign colleagues or by scientists in other countries.

Appendix B gives an overview of the major funding mechanisms through which the NIH supports these diverse activities. All foreign requests for NIH awards undergo the same stringent peer review process as do domestic applications for NIH support. Research proposals must justify the need for NIH international projects to be carried out overseas or by foreign scientists.

Many international activities are conducted under bilateral agreements between the United States and other governments. These agreements, usually established through the U.S. Department of State, may have a broad science and technology scope or a specific health focus. Table I-1 provides a list of international agreements involving the NIH. International activities also include NIH participation in meetings, conferences, and workshops, many of which are sponsored by multinational organizations such as the World Health Organization (WHO) and the Pan American Health Organization (PAHO).

Table I-2 shows total expenditures for NIH international programs by activity and component for fiscal year 1998 (FY 98). During FY 98, the NIH expended $219.2 million of its appropriated funds on international activities. That sum represented about 1.6% of the NIH's $13.7 billion budget for FY 98.

For FY 98, the funding breakdown included $108.7 million for research awards (including $88.7 million for grants and $20.0 million for contracts); $96.8 million for scientist awards ($85.8 million for foreign scientists in the United States, $3.8 million for U.S. scientists abroad, and $7.2 million for bilateral exchanges including conferences); $3.8 million for travel; and $9.9 million for program support. This funding distribution is summarized in Figure I-1. The annual NIH budgets for international expenditures from FY 85 through FY 98 are summarized in Figure I-2.

Table I-3 lists NIH expenditures during FY 98 for research and training awards by country or area and by type of award. In addition to awards to scientists at foreign institutions, the NIH awarded approximately 5.1 million in grants, contracts, and cooperative agreements to multilateral organizations in FY 98.

Table I-4 provides a historical summary of NIH support for international research and training awards (excluding travel and program support) since FY 50. In recent years, although the numbers of foreign grants have decreased, there has been a precipitous rise in the numbers of domestic grants with foreign components. This increase demonstrates the increase in collaboration between U.S. and foreign investigators.

John E. Fogarty International Center for Advanced Study in the Health Sciences

In a collaborative study sponsored by the John E. Fogarty International Center (FIC) for Advanced Study in the Health Sciences, scientists from Georgetown University, Washington, D.C., are working with scientists at the University of Yaoundé, Cameroon, to study immune system dysfunction in malaria and concomitant measles. Mortality in measles outbreaks in malaria-plagued areas of Cameroon often has been associated with secondary bacterial infections. Lower levels of measles antibodies have been observed in persons with malaria parasitemia than in persons who were parasite negative. These findings have important public health indications for the endemic area, because measles vaccination is probably less effective if given during the season of high malaria incidence than at other times of the year. Persons who are vaccinated for measles at Yaoundé hospital will be invited to return and have their blood drawn at regular intervals, and efforts will be made to determine the levels and duration of measles antibodies and malarial antibodies, as well as other indicators of immune system responses. It is hoped that this work will provide enough data to form the basis for the most effective and efficient vaccination regimens.

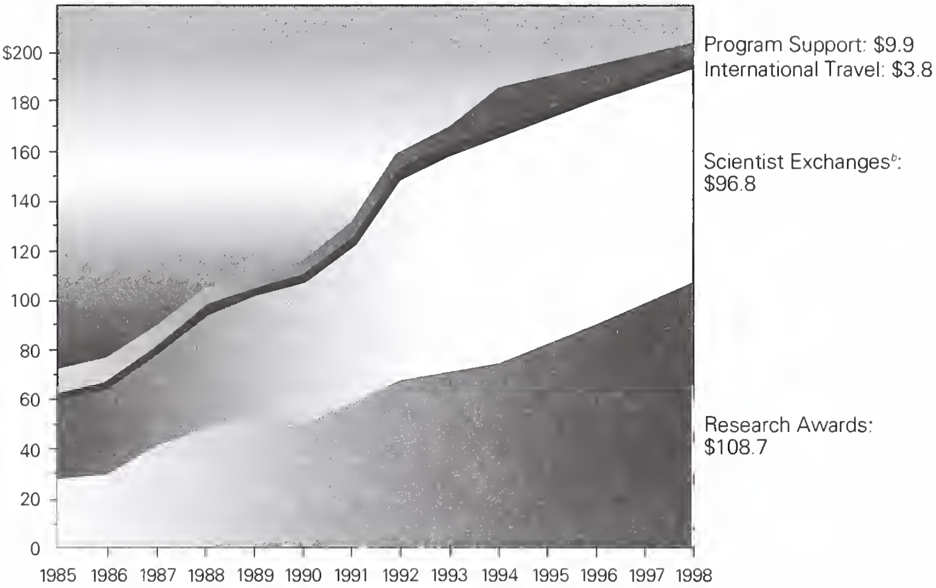
Investigators at the University of California, Santa Cruz, are collaborating with scientists at the University of the South Pacific, Suva, Fiji, to study possible antitumor compounds from the biologically important marine sponge *Jaspis coriacea*, which contains

TABLE I-2.
Total Expenditures for NIH International Programs by Activity and NIH Component, Fiscal Year 1998 (in thousands of dollars)

	NCI	NHLBI	NIDR	NIDDK	NINDS	NIAID	NIGMS	NICHD	NEI	NIEHS	NIA	NIAMS
Research Awards												
Grants												
Foreign Research Grants	10,644	2,234	753	1,814	2,267	4,386	939	989	1,671	280	881	175
Foreign Components of Domestic Grants	9,149	3,831	704	1,971	2,828	12,249	532	3,533	90	1,474	3,394	915
Subtotal	19,793	6,065	1,457	3,785	5,095	16,635	1,471	4,522	1,761	1,754	4,275	1,090
Contracts												
Foreign Contracts	5,068	32	—	—	730	902	—	1,758	373	498	—	—
Foreign Components of Domestic Contracts	2,363	960	—	—	—	5,622	—	247	—	—	—	—
Subtotal	7,431	992	—	—	730	6,524	—	2,005	373	498	—	—
Scientist Awards												
Foreign Scientists												
Intramural Research Program	14,373	5,634	2,308	6,859	4,807	7,029	—	5,887	1,756	2,977	2,325	1,892
Research Fellowships	—	—	—	—	—	—	—	—	—	—	—	—
Scholars-in-Residence	—	—	—	—	—	—	—	—	—	—	—	—
International Training and Research Grants	—	—	604	—	—	1,316	—	333	—	150	113	—
Subtotal	14,373	5,634	2,912	6,859	4,807	8,345	—	6,220	1,756	3,127	2,438	1,892
U.S. Scientists												
Research Fellowships/Work Study	116	25	—	11	26	30	92	56	—	—	—	—
Minority International Res. Training Program	—	—	—	—	—	—	—	—	—	—	—	—
Subtotal	116	25	—	11	26	30	92	56	—	—	—	—
Bilateral Exchanges/Conferences	2,046	380	92	362	34	60	—	214	166	594	208	93
International Travel	805	23	227	88	188	757	—	232	91	115	139	48
ICD Program Support	1,220	497	216	14	—	145	—	50	56	125	117	3
Total NIH	45,784	13,616	4,904	11,119	10,880	32,496	1,563	13,299	4,203	6,213	7,177	3,126
Special Foreign Currency[a]	250	125	—	—	84	227	180	—	132	—	—	—
Grand Total	46,034	13,741	4,904	11,119	10,964	32,723	1,743	13,299	4,335	6,213	7,177	3,126

[a] *Public Law 480 Funds are appropriated to the Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services, and awarded and administered*

FIGURE I-2.
NIH International Research Awards, Scientist Awards, Travel, and Program Support, Fiscal Years 1985–1998[a] (in millions of dollars)



[a] *Excludes $1.3 million of Special Foreign Currency Program funding.*
[b] *Since fiscal year 1989, expenditures for "Bilateral Exchanges/Conferences" have been reported under "Scientist Exchanges." In previous NIH annual reports, they were listed under "Program Support." All figures were made comparable for this graph.*

compounds that have been shown to kill breast tumor cells in vitro. *J. coriacea* is common throughout the Indo-Pacific region and is especially abundant in reefs throughout the Fiji Islands. Previous work has established that distribution of the types of compounds found in *J. coriacea* samples appear to vary with the season and with geographic location, but the factors that cause variability are not understood. This study, supported by a Fogarty International Research Collaboration Award, will examine *J. coriacea* in greater detail, including the chemical variation of its antitumor compounds as a function of ecological factors.

In a study cosponsored by FIC, researchers at the Ministry of Health and Makerere University, Kampala, Uganda, and the Centers for Disease Control and Prevention are collaborating with scientists at Case Western Reserve University, Cleveland, Ohio. These investigators have made significant progress toward developing practical and affordable prevention measures to reduce the burden of tuberculosis in HIV-infected adults who were

														Funds Expended	
NIDCD	NIMH	NIDA	NIAAA	NINR	NCRR	NHGRI	FIC	NLM	OD	CC	CIT	CSR	TOTALS	U.S.	Abroad
201	2,360	2,948	268	364	55	79	—	—	—	—	—	—	33,308	—	X
582	3,885	1,774	1,036	552	546	233	5,854	94	117	—	—	—	55,343	—	X
783	6,245	4,722	1,304	916	601	312	5,854	94	117	—	—	—	88,651	—	X
—	40	—	45	—	158	364	—	—	—	—	—	—	9,968	—	X
—	—	—	—	—	30	860	—	—	—	—	—	—	10,082	—	X
—	40	—	45	—	188	1,224	—	—	—	—	—	—	20,050	—	X
778	3,469	714	468	—	5	1,971	—	1,205	132	1,621	80	—	66,290	X	—
—	—	296	—	—	—	—	808	—	—	—	—	—	1,104	X	—
—	—	—	—	—	—	—	249	—	—	—	—	—	249	X	—
—	500	125	—	—	—	—	13,700	—	1,297	—	—	—	18,138	X	—
778	3,969	1,135	468	—	5	1,971	14,757	1,205	1,429	1,621	80	—	85,781	X	—
—	112	—	16	—	—	—	611	—	—	—	—	—	1,095	—	X
—	—	—	—	—	—	—	—	—	2,700	—	—	—	2,700	—	X
—	112	—	16	—	—	—	611	—	2,700	—	—	—	3,795	—	X
375	78	76	191	—	4	610	67	20	1,562	—	—	—	7,232	X	X
6	281	97	61	9	18	280	51	75	118	54	9	16	3,788	X	X
5	—	148	135	—	—	—	6,853	280	9	—	—	—	9,873	X	—
1,947	10,725	6,178	2,220	925	816	4,397	28,193	1,674	5,935	1,675	89	16	219,170	X	X
—	129	151	—	—	—	—	—	—	—	—	—	—	1,278	—	X
1,947	10,854	6,329	2,220	925	816	4,397	28,193	1,674	5,935	1,675	89	16	220,448	X	X

by the NIH.

positive for purified protein derivative (PPD). The study indicates that a 3- to 6-month course of prophylactic treatment for tuberculosis in a study population of HIV-infected adults significantly reduced the risk of active infection and transmission.

National Institute on Aging

The National Institute on Aging's Office of Demography of Aging (ODA) helped to draft the communiqué for the Denver G8 Economic Summit Meeting in May–June 1997. ODA's major contributions were to highlight current research issues related to population aging, projections, retirement, disability trends, and cross-national research opportunities and to stress the need for appropriate and comparable data. The last paragraph of the final communiqué on population aging reflects the success of ODA in these efforts:

> We agreed that it is important to learn from one another how our policies and programs can promote active aging and advance structural reforms to preserve and strengthen our pension, health, and long-term care systems. Our governments will work together, within the OECD [Organization for Economic Cooperation and Development] and with other international organizations, to promote active aging through information exchanges and cross-national research. We encourage collaborative biomedical and behavioral research to improve active life expectancy and reduce disability and have directed our officials to identify gaps in our knowledge and explore developing comparable data in our nations to improve our capacity to address the challenges of population aging into the 21st century.

This language has acted as a powerful catalyst and has spurred several international organizations and some national governments to make research on population aging a higher priority in their agendas.

The Neuroscience and Neuropsychology of Aging Program supported collaboration between investigators from the University of Colorado Health Sciences Center, Denver, and the Karolinska Institute, Stockholm, Sweden, which provided insights into neuronal survival and maintenance of neural circuits throughout life. The researchers mapped the pattern of gene expression for two related neurotrophic factors (neurturin and neurotrophic factor derived from a glial cell line) and for specific receptor proteins for these factors in the developing and adult nervous system of rodents. Findings suggested multiple independent and overlapping roles for these two neurotrophic factors in the developing and adult organism. Continued exploration of the synthesis, localization, and biological effects of these factors and their receptor molecules in the adult and aging nervous system will contribute to understanding of the role of such factors in health and disease and will guide development of treatment strategies based on neurotrophic factors.

TABLE I-3.

NIH International Research and Research Training Awards[a] by Country/Area and Mechanism, Fiscal Year 1998 (in thousands of dollars)

Country/Area	Research Grants		Research Contracts		Foreign Components of Domestic Awards		Special Foreign Currency Program Public Law 480		Visiting Program	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Albania	—	—	—	—	—	—	—	—	1	30
Algeria	—	—	—	—	—	—	—	—	2	33
Argentina	1	60	—	—	14	325	—	—	22	640
Armenia	—	—	—	—	—	—	—	—	1	39
Australia	10	2,658	1	498	22	2,142	—	—	39	996
Austria	—	—	—	—	4	109	—	—	9	119
Bahamas	—	—	—	—	—	—	—	—	—	—
Bangladesh	1	48	—	—	4	782	—	—	5	126
Barbados	—	—	—	—	—	—	—	—	—	—
Belarus	—	—	1	50	1	20	—	—	4	115
Belgium	1	150	—	—	8	335	—	—	8	256
Bolivia	—	—	—	—	—	—	—	—	—	—
Bosnia	—	—	—	—	—	—	—	—	1	43
Botswana	—	—	—	—	1	23	—	—	—	—
Brazil	1	574	—	—	15	824	—	—	25	695
Bulgaria	—	—	—	—	2	49	—	—	7	296
Burkina Faso	—	—	—	—	—	—	—	—	1	32
Cambodia	—	—	—	—	1	15	—	—	—	—
Cameroon	—	—	—	—	10	505	—	—	—	—
Canada	94	15,654	6	1,968	157	10,726	—	—	123	3,855
Chile	—	—	—	—	9	464	—	—	7	196
China	2	594	7	832	41	3,659	—	—	262	6,524
Colombia	—	—	—	—	5	346	—	—	5	184
Congo	—	—	—	—	—	—	—	—	1	32
Costa Rica	—	—	1	931	5	216	—	—	—	—
Croatia	—	—	—	—	4	92	—	—	6	143
Cuba	—	—	—	—	—	—	—	—	1	12
Cyprus	—	—	—	—	—	—	—	—	2	67
Czech Republic	—	—	—	—	11	256	—	—	11	355
Denmark	3	732	—	—	14	518	—	—	10	344
Dominican Republic	—	—	—	—	3	137	—	—	—	—
Ecuador	—	—	—	—	1	25	—	—	—	—
Egypt	—	—	—	—	3	112	—	—	2	40
El Salvador	—	—	—	—	1	5	—	—	—	—
Estonia	—	—	—	—	4	76	—	—	2	76
Ethiopia	—	—	—	—	2	220	—	—	2	72
Fiji	—	—	—	—	1	25	—	—	1	29
Finland	3	511	2	364	7	344	—	—	20	523
France	2	511	2	98	16	497	—	—	87	2,332
Gabon	—	—	—	—	—	—	—	—	—	—
The Gambia	—	—	—	—	3	150	—	—	—	—
Georgia	—	—	—	—	—	—	—	—	1	7
Germany	—	—	2	85	21	1,432	—	—	109	3,008
Ghana	—	—	—	—	5	1,328	—	—	—	—
Greece	—	—	—	—	—	—	—	—	14	507
Guadeloupe	—	—	—	—	—	—	—	—	—	—
Guatemala	—	—	—	—	1	5	—	—	—	—
Haiti	—	—	—	—	2	475	—	—	—	—
Hong Kong	—	—	—	—	1	269	—	—	4	111
Honduras	—	—	—	—	1	5	—	—	—	—
Hungary	—	—	—	—	11	251	—	—	23	700
Iceland	—	—	—	—	—	—	—	—	2	60
India	3	118	—	—	14	743	15	1,053	105	2,782
Indonesia	—	—	—	—	5	839	—	—	—	—
Iran	—	—	—	—	—	—	—	—	5	82
Iraq	—	—	—	—	—	—	—	—	—	—
Ireland	—	—	1	1,009	2	494	—	—	4	149
Israel	14	1,991	—	—	27	1,560	—	—	49	1,872
Italy	4	881	—	—	21	772	—	—	126	3,519
Jamaica	—	—	1	1,042	2	40	—	—	1	32
Japan	—	—	2	340	9	910	—	—	300	7,986
Jordan	—	—	—	—	1	7	—	—	2	44
Kenya	—	—	—	—	10	751	—	—	—	—
Korea	—	—	—	—	2	99	—	—	142	3,509
Laos	—	—	—	—	4	83	—	—	—	—
Latvia	—	—	—	—	1	5	—	—	1	36
Lebanon	—	—	—	—	—	—	—	—	1	33
Lithuania	—	—	—	—	1	15	—	—	—	—
Luxembourg	—	—	—	—	1	12	—	—	—	—
Macedonia	—	—	—	—	—	—	—	—	—	—
Madagascar	—	—	—	—	4	176	—	—	—	—
Malawi	—	—	—	—	3	512	—	—	1	31
Malaysia	—	—	—	—	1	540	—	—	2	56
Mali	1	649	—	—	4	736	—	—	2	45

Special Volunteers and Guest Researchers[b]	International Research Fellows		Senior International Fellows		National Research Service Award		
No.	No.	Amount	No.	Amount	No.	Amount	Totals
—	—	—	—	—	—	—	30
2	—	—	—	—	—	—	33
2	2	62	—	—	—	—	1,087
—	1	36	—	—	—	—	75
10	—	—	2	42	—	—	6,336
6	—	—	—	—	—	—	228
—	—	—	—	—	—	—	0
1	—	—	—	—	—	—	956
—	—	—	—	—	—	—	0
—	1	32	—	—	—	—	217
2	—	1	—	—	—	—	761
1	—	—	—	—	—	—	0
2	—	—	—	—	—	—	43
—	—	—	—	—	—	—	23
26	1	35	—	—	—	—	2,128
—	1	37	—	—	—	—	282
—	—	—	—	—	—	—	32
—	—	—	—	—	—	—	15
—	—	—	—	—	—	—	505
17	—	—	—	—	8	187	32,390
3	1	33	—	—	—	—	693
44	—	—	—	—	—	—	11,609
4	—	—	—	—	—	—	530
—	—	—	—	—	—	—	32
1	—	—	—	—	—	—	1,147
—	—	—	—	—	—	—	235
—	—	—	—	—	—	—	12
—	—	—	—	—	—	—	67
2	1	25	—	—	—	—	636
9	—	—	—	—	—	—	1,594
—	—	—	—	—	—	—	137
1	—	—	—	—	—	—	25
1	—	—	—	—	—	—	152
—	—	—	—	—	—	—	5
—	—	—	—	—	—	—	152
1	—	—	—	—	—	—	292
—	—	—	—	—	—	—	54
7	—	—	—	—	—	—	1,742
17	1	32	5	159	3	64	3,693
—	—	—	1	34	—	—	0
—	—	—	—	—	—	—	150
—	—	—	—	—	—	—	7
75	—	—	4	134	1	26	4,685
—	—	—	—	—	—	—	1,328
8	2	60	—	—	—	—	567
—	—	—	—	—	—	—	0
—	—	—	—	—	—	—	5
—	—	—	—	—	—	—	475
—	—	—	—	—	—	—	380
—	—	—	—	—	—	—	5
8	4	139	—	—	—	—	1,090
—	—	—	—	—	—	—	60
14	1	50	—	—	—	—	4,746
—	—	—	—	—	—	—	839
3	—	—	—	—	—	—	82
—	—	—	—	—	—	—	0
1	—	—	—	—	—	—	1,652
10	—	—	—	—	—	—	5,423
40	—	—	—	—	—	—	5,172
1	—	—	—	—	—	—	1,114
138	—	—	—	—	—	—	9,236
1	—	—	—	—	—	—	51
—	—	—	—	—	—	—	751
37	—	—	—	—	—	—	3,608
—	—	—	—	—	—	—	83
—	—	—	—	—	—	—	41
2	—	—	—	—	—	—	33
—	—	—	—	—	—	—	15
—	—	—	—	—	—	—	12
1	—	—	—	—	—	—	0
—	—	—	—	—	—	—	176
—	—	—	—	—	—	—	543
—	—	—	—	—	—	—	596
—	—	—	—	—	—	—	1,430

Cont'd

National Institute on Alcohol Abuse and Alcoholism

South Africa

The active membership of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in the Health Working Group of the Gore-Mbeki Binational Commission for South Africa has led to significant progress in research on fetal alcohol syndrome (FAS) and in efforts to develop research on prevention and treatment of alcoholism. Studies addressing the problem of FAS are supported jointly by NIAAA and the Office of Research on Minority Health, NIH. The South African government recognized that FAS is particularly prevalent in workers on farms and in vineyards of the Western Cape Province and is working with NIAAA on research projects and prevention strategies. The high prevalence of this syndrome in farmworkers derives from a culture of heavy alcohol drinking. This culture developed as a consequence of past practices of providing partial wages to farmworkers in the form of alcohol. A prevalence rate of 5% (50 per 1,000) was documented in the city of Wellington in the western cape, compared with estimates of 0.5B3 per 1,000 in the United States.

Russia

The NIAAA Director is the lead for alcohol-related problems, on the Gore-Primakov Commission Subcommittee for Joint Activities on Identified Health Issues. Alcoholism is a significant problem in Russia, and work is focusing on three areas: (1) prevention and treatment of alcohol-use disorders in the primary care setting; (2) prevention of alcohol-related problems in adolescents; and (3) prevention and treatment of alcohol-related birth defects.

After 2 years of study, investigators at the University of Minnesota School of Public Health, Minneapolis, and two Russian researchers in prevention, from Moscow, completed evaluation of a school- and community-based intervention for prevention of alcohol problems in preteens in Russia. The intervention was used in fifth graders from 26 public schools in Moscow and their parents. An important finding from baseline measures of 1,300 children was that children in Russia are likely to initiate alcohol use at a very early age: 43% reported alcohol use by the spring of their fifth-grade year.

Table I-3 Contd.

TABLE I-3.

NIH International Research and Research Training Awards[a] by Country/Area and Mechanism, Fiscal Year 1998 (in thousands of dollars)

	Research Grants		Research Contracts		Foreign Components of Domestic Awards		Special Foreign Currency Program (P.L. 480)		Visiting Program	
Country/Area	**No.**	**Amount**	**No.**	**Amount**	**No.**	**Amount**	**No.**	**Amount**	**No.**	**Amount**
Mauritius	—	—	—	—	—	—	—	—	—	—
Mexico	1	93	—	—	31	1,899	—	—	15	329
Mongolia	—	—	—	—	1	33	—	—	1	35
Morocco	—	—	—	—	—	—	—	—	4	102
Namibia	—	—	—	—	1	24	—	—	—	—
Nepal	—	—	—	—	1	61	—	—	—	—
The Netherlands	2	187	—	—	14	514	—	—	25	738
New Zealand	2	168	2	448	10	654	—	—	6	144
Nicaragua	—	—	—	—	1	5	—	—	—	—
Nigeria	—	—	—	—	7	649	—	—	3	108
Norway	—	—	1	49	2	55	—	—	1	53
Pakistan	—	—	—	—	1	205	—	—	10	207
Palau	—	—	—	—	—	—	—	—	—	—
Panama	—	—	—	—	8	398	—	—	—	—
Papua New Guinea	—	—	—	—	1	30	—	—	—	—
Peru	—	—	—	—	11	561	—	—	2	41
Philippines	—	—	—	—	3	185	—	—	8	214
Poland	—	—	—	—	8	367	5	225	28	731
Portugal	—	—	—	—	3	685	—	—	5	153
Romania	—	—	—	—	—	—	—	—	4	94
Russia	—	—	—	—	33	1,046	—	—	88	2,969
Rwanda	—	—	—	—	—	—	—	—	—	—
St. Kitts and Nevis	—	—	—	—	4	783	—	—	—	—
Saudi Arabia	—	—	—	—	—	—	—	—	—	—
Scotland	—	—	—	—	—	—	—	—	—	—
Senegal	—	—	—	—	3	264	—	—	1	31
Serbia	—	—	—	—	—	—	—	—	2	34
Seychelles	—	—	—	—	1	25	—	—	—	—
Sierra Leone	—	—	—	—	—	—	—	—	1	34
Singapore	—	—	—	—	1	21	—	—	4	141
Slovakia	—	—	—	—	3	81	—	—	18	496
Slovenia	—	—	—	—	3	70	—	—	1	61
South Africa	1	118	—	—	11	780	—	—	1	32
Spain	1	56	—	—	7	606	—	—	49	1,269
Sri Lanka	—	—	—	—	—	—	—	—	2	77
Sudan	—	—	—	—	1	10	—	—	—	—
Suriname	—	—	—	—	4	126	—	—	—	—
Swaziland	—	—	—	—	—	—	—	—	1	38
Sweden	6	1,298	1	505	27	2,954	—	—	11	252
Switzerland	—	—	—	—	14	1,113	—	—	10	226
Tanzania	—	—	—	—	3	229	—	—	—	—
Thailand	—	—	—	—	12	1,985	—	—	8	200
Trinidad	—	—	—	—	1	22	—	—	1	36
Tunisia	—	—	—	—	—	—	—	—	1	17
Turkey	—	—	—	—	3	58	—	—	15	434
Uganda	—	—	—	—	7	2,368	—	—	—	—
Ukraine	—	—	—	—	3	84	—	—	10	326
United Kingdom	26	4,027	4	631	71	4,466	—	—	87	2,361
United States	—	—	—	—	—	—	—	—	218	10,682
Uruguay	—	—	—	—	1	25	—	—	—	—
Uzbekistan	—	—	—	—	—	—	—	—	1	44
Venezuela	—	—	—	—	4	650	—	—	2	65
Vietnam	—	—	1	235	6	175	—	—	3	89
Yugoslavia	—	—	—	—	1	130	—	—	1	24
Zaire	—	—	—	—	—	—	—	—	—	—
Zambia	—	—	—	—	4	1,170	—	—	—	—
Zimbabwe	—	—	—	—	5	1,064	—	—	1	18
Taiwan	—	—	—	—	10	766	—	—	22	612
Subtotal	179	31,078	35	9,085	869	62,472	20	1,278	2,232	66,290
International Organizations										
EORTC	1	390	—	—	—	—	—	—	—	—
IARC	1	391	—	—	—	—	—	—	—	—
PAHO	—	—	1	420	—	—	—	—	—	—
UICC	—	—	1	90	—	—	—	—	—	—
WHO	2	1,449	1	373	—	—	—	—	—	—
HFSP	—	—	—	—	—	2,000	—	—	—	—
Subtotal	4	2,230	3	883	—	2,000	—	—	—	—
Total	183	33,308	38	9,968	869	64,472	20	1,278	2,232	66,290

[a] *Does not include Scholars-in-Residence Awards ($0.2 million), International Training and Research Grants ($18.1 million), Minority International Research Training Program ($2.7 million), part of FIC's Biodiversity Program ($0.8 million) ICD Program Support/Travel ($13.7 million), and Bilateral Exchanges ($7.2 million). Most of the funds for these programs are expended in the United States.*

Special Volunteers and Guest Researchers[b]	International Research Fellows		Senior International Fellows		National Research Service Award		
No.	No.	Amount	No.	Amount	No.	Amount	Totals
—	—	—	—	—	—	—	0
1	3	95	—	—	—	—	2,416
—	—	—	—	—	—	—	68
1	—	—	—	—	—	—	102
—	—	—	—	—	—	—	24
—	—	—	—	—	—	—	61
21	—	—	1	32	—	—	1,471
2	—	—	—	—	—	—	1,414
—	—	—	—	—	—	—	5
1	2	82	—	—	—	—	839
2	—	—	—	—	—	—	157
—	—	—	—	—	—	—	412
—	—	—	—	—	—	—	0
—	—	—	—	—	—	—	398
—	—	—	—	—	—	—	30
—	—	—	—	—	—	—	602
2	—	—	—	—	—	—	399
4	5	162	—	—	—	—	1,485
2	—	—	—	—	—	—	838
1	1	36	—	—	—	—	130
6	1	30	—	—	—	—	4,045
—	—	—	—	—	—	—	0
—	—	—	—	—	—	—	783
2	—	—	—	—	—	—	0
—	—	—	1	23	—	—	23
—	—	—	—	—	—	—	295
—	—	—	—	—	—	—	34
—	—	—	—	—	—	—	25
—	—	—	—	—	—	—	34
—	—	—	—	—	—	—	162
1	—	—	—	—	—	—	577
1	—	—	—	—	—	—	131
1	—	—	—	—	—	—	930
22	—	—	1	49	—	—	1,980
1	—	—	—	—	—	—	77
—	—	—	—	—	—	—	10
—	—	—	—	—	—	—	126
—	—	—	—	—	—	—	38
4	—	—	2	65	1	22	5,096
7	—	—	1	42	—	—	1,381
—	—	—	—	—	—	—	229
1	1	37	—	—	—	—	2,222
2	—	—	—	—	—	—	58
—	—	—	—	—	—	—	17
3	1	35	—	—	—	—	527
—	—	—	—	—	—	—	2,368
1	1	49	—	—	—	—	459
24	—	—	4	65	8	185	11,735
1	—	—	—	—	—	—	10,682
—	—	—	—	—	—	—	25
—	—	—	—	—	—	—	44
—	—	—	—	—	—	—	715
—	—	—	—	—	—	—	499
—	—	—	—	—	—	—	154
—	—	—	—	—	—	—	0
—	—	—	—	—	—	—	1,170
1	1	37	—	—	—	—	1,119
8	—	—	—	—	—	—	1,378
621	32	1,104	21	611	21	484	172,402
—	—	—	—	—	—	—	390
—	—	—	—	—	—	—	391
—	—	—	—	—	—	—	420
—	—	—	—	—	—	—	90
—	—	—	—	—	—	—	1,822
—	—	—	—	—	—	—	2,000
—	—	—	—	—	—	—	5,113
621	32	1,104	21	611	21	484	177,515

[b] *Do not receive NIH funding.*

Findings from the outcome measures indicate that parents and children participated in the program at very high rates, comparable to rates seen among U.S. families who participated in a similar program. Children in the intervention program reported having more family rules against drinking of alcohol than control children did, and those in the program did not think their parents would allow them to drink when they were seniors in high school. Furthermore, there was a statistically significant increase in knowledge about alcohol and its effects for children in the intervention group.

Evidence from studies conducted throughout the world shows that primary care physicians can have a substantial effect on the reduction of alcohol use by their patients, before serious problems and addiction occur. Brief intervention delivered by physicians in primary care settings may be beneficial to the heavily stressed Russian health care delivery system, because its implementation does not involve new medications or expensive treatment. This intervention can be accomplished by providing training to practicing clinicians, residents, and medical students. A course for 40 faculty from four medical academies in St. Petersburg focused on the role of primary care physicians in providing screening and brief intervention for misuse of alcohol by patients. The 5-day course was taught by teams of U.S. and Russian faculty from Harvard University Medical School, Boston, Massachusetts; Yale University Medical School, New Haven, Connecticut; the University of Wisconsin, Madison; Pavlov State Medical University, St. Petersburg; and St. Petersburg Post Graduate Academy for Medical Studies. Changes in clinical and teaching practices of the participants will be measured to determine the effectiveness of the course. As a direct result of this activity, a course in alcohol-use disorders was added to the primary care curriculum of Pavlov State Medical University.

In Russia, investigators have started work in improving the diagnosis of FAS and in shaping and adapting instruments to determine the extent of maternal alcohol use and to conduct neurobehavioral assessments in children. Russian psychologists and physicians have been trained by U.S. experts, and studies of risk factors for maternal misuse of

TABLE I-4.
NIH International Research and Research Training Awards, Fiscal Years 1950–1998 (in thousands of dollars)

		Research Grants		Research Contracts		Foreign Components of Domestic Awards		Special Foreign Currency Program (Public Law 480)		Training Grants	
Fiscal Year	Total	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
1950	391	20	219	—	—	—	—	—	—	—	—
1951	412	28	210	—	—	—	—	—	—	—	—
1952	495	22	257	—	—	—	—	—	—	—	—
1953	495	24	245	—	—	—	—	—	—	—	—
1954	497	15	145	—	—	—	—	—	—	—	—
1955	470	14	111	—	—	—	—	—	—	—	—
1956	683	18	190	—	—	—	—	—	—	—	—
1957	1,808	61	824	—	—	—	—	—	—	1	13
1958	2,777	92	1,307	—	—	—	—	—	—	1	17
1959	5,425	170	2,997	—	—	—	—	—	—	2	30
1960	8,492	307	5,249	3	90	—	—	—	—	3	39
1961	12,692	563	8,999	2	118	—	—	—	—	7	251
1962	22,770	811	13,410	8	181	5	2,093	20	2,765	13	380
1963	24,067	981	14,956	5	182	7	2,093	16	1,517	16	536
1964	25,590	932	13,759	13	429	6	2,484	19	3,328	17	544
1965	23,514	801	11,467	22	867	6	2,491	25	3,026	22	615
1966	21,653	718	10,010	29	901	5	2,423	22	2,182	18	559
1967	20,068	624	8,509	27	1,037	5	2,360	27	3,559	15	506
1968	20,525	480	6,424	35	1,325	5	2,360	42	5,459	16	449
1969	19,985	325	4,481	32	1,369	5	2,294	44	7,312	11	187
1970	15,627	170	2,968	34	1,805	4	2,070	39	4,503	4	6
1971	21,844	120	2,489	41	2,319	5	2,285	79	10,149	—	—
1972	19,762	113	2,449	65	5,337	4	2,399	24	2,894	—	—
1973	19,874	116	2,905	86	6,508	4	2,244	21	2,706	—	—
1974	23,020	119	3,360	105	8,381	4	2,360	13	1,544	—	—
1975	31,867	130	3,917	120	13,790	4	2,411	24	3,257	—	—
1976	34,457	138	5,128	134	12,525	4	2,400	18	2,934	—	—
1977	40,719	149	6,532	135	15,173	4	2,400	25	4,484	—	—
1978	42,829	162	7,502	139	15,107	4	2,117	16	4,199	—	—
1979	47,333	191	10,042	117	14,759	13	4,699	9	1,298	—	—
1980	45,179	206	11,139	93	12,932	10	2,756	9	612	—	—
1981	46,622	237	13,223	61	9,672	10	2,585	20	911	—	—
1982	45,598	212	13,336	53	10,608	8	2,384	19	1,424	—	—
1983	46,023	214	14,079	37	6,597	9	2,741	14	945	—	—
1984	60,227	191	15,708	43	11,094	9	2,870	39	6,128	—	—
1985	59,047	220	15,466	55	8,767	10	2,998	47	4,560	—	—
1986	58,385	219	16,723	63	9,276	9	2,933	29	998	—	—
1987	71,193	242	22,150	55	11,658	9	3,019	63	1,848	—	—
1988	78,028	256	26,405	52	13,338	9	2,336	59	622	12	3,912
1989	90,710	259	27,627	50	14,733	142	9,723	21	2,329	14	4,322
1990	95,819	220	26,828	57	11,337	188	13,015	24	1,290	14	4,733
1991	116,954	213	27,406	48	16,623	252	15,423	21	1,332	14	5,142
1992	142,792	210	29,270	51	24,028	337	21,306	19	2,718	14	5,178
1993	154,938	240	35,928	43	16,715	450	23,504	22	1,493	17	5,114
1994	166,169	231	33,254	59	17,647	481	27,430	25	1,493	41	13,505
1995	171,389	202	31,043	60	15,063	527	34,061	29	1,534	62	17,602
1996	178,658	184	32,818	65	14,285	572	41,284	20	978	67	19,085
1997	186,200	168	33,885	49	11,258	894	54,183	21	1,511	82	17,818
1998	199,555	183	33,308	38	9,968	869	65,425	20	1,278	89	20,838

[a] *Table I-4 includes only those categories in Table I-2 that constitute research and research training awards.*

alcohol and prevalence of FAS are under way.

Mexico

Joint research that started 3 years ago among scientists at the Institute of Nutrition, Mexico City, Thomas Jefferson University, Philadelphia, Pennsylvania, and Johns Hopkins University, Baltimore, Maryland, has identified a possible mitigating factor for the high rates of death from liver disease in certain districts in Mexico. A traditional alcoholic drink known as pulque, which is made from cactus and is consumed in high quantities in these districts, was identified as a source of endotoxin and live gram-negative pathogenic bacteria, such as *Salmonella* and *Yersinia*. As a result, the Mexican Ministry of Health initiated a commission to investigate the safety and to monitor the production of this beverage.

Visiting Program		Special Volunteers and Guest Researchers[b]	International Research Fellows		Scholars-in-Residence		Senior International Fellows		National Research Service Awards	
No.	Amount	No.	No.	Amount	No.	Amount	No.	Amount	No.	Amount
1	—	—	36	135	—	—	—	—	11	37
5	29	—	37	127	—	—	—	—	13	47
7	42	—	36	119	—	—	—	—	20	78
6	42	—	13	41	—	—	—	—	36	168
17	115	—	2	1	—	—	—	—	54	236
26	165	—	—	—	—	—	—	—	48	194
42	270	—	—	—	—	—	—	—	56	224
76	518	—	—	—	—	—	—	—	86	453
110	785	—	16	102	—	—	—	—	99	566
128	1,097	—	67	467	—	—	—	—	128	834
138	1,035	—	68	501	—	—	—	—	230	1,577
149	869	—	—	—	—	—	—	—	251	1,780
190	1,052	—	90	681	—	—	—	—	279	2,207
200	1,203	—	172	1,199	—	—	—	—	310	2,381
179	1,434	—	183	1,199	—	—	—	—	296	2,413
156	1,172	—	166	1,199	—	—	—	—	342	2,678
139	1,194	—	166	1,197	—	—	—	—	397	3,188
129	1,157	87	176	1,200	—	—	—	—	211	1,740
149	1,405	95	151	1,379	—	—	—	—	188	1,724
138	1,299	93	168	1,409	5	130	—	—	222	1,504
178	1,628	53	137	1,027	5	119	—	—	185	1,101
188	2,070	100	130	1,077	6	141	—	—	167	1,314
259	3,108	118	163	1,588	8	182	—	—	214	1,806
290	3,763	134	110	777	12	228	—	—	143	742
351	4,506	145	127	1,489	13	219	—	—	129	1,162
494	5,946	157	107	1,370	8	163	—	—	115	1,014
676	7,948	180	137	1,605	8	150	42	717	75	1,050
740	8,404	159	126	1,636	16	362	50	906	59	823
804	9,469	205	128	2,094	12	253	64	1,203	75	1,065
830	11,159	229	134	2,413	11	272	75	1,680	72	1,009
909	12,445	266	132	2,263	20	715	52	1,227	54	1,090
976	14,568	355	136	3,450	18	456	32	673	58	1,084
979	15,722	381	153	3,061	20	485	29	593	59	985
1,128	16,953	390	101	2,689	8	357	41	926	43	756
1,176	19,654	396	87	2,357	12	565	53	1,240	34	611
1,288	21,882	479	104	2,794	10	402	45	1,165	48	1,013
1,391	23,659	551	101	2,727	14	446	40	868	34	755
1,465	27,796	538	103	2,767	6	279	47	921	36	755
1,507	31,539	410	97	2,664	11	329	44	998	39	797
1,470	32,106	623	91	2,472	12	381	38	926	34	794
1,555	37,650	666	146	3,963	8	188	41	833	36	903
1,680	44,525	684	157	4,136	7	478	39	1,077	33	812
1,866	53,257	635	146	4,518	7	680	49	1,235	26	602
2,171	66,105	669	124	3,835	5	618	53	1,179	19	447
2,199	68,518	627	74	2,289	6	650	42	861	23	522
2,152	67,960	630	55	1,759	13	665	44	1,124	23	578
2,174	67,059	660	39	1,306	7	536	24	777	21	520
2,210	64,192	622	39	1,316	2	563	26	904	22	570
2,232	66,290	621	32	1,104	1	249	21	611	21	484

[b] *Do not receive NIH funding.*

National Institute of Allergy and Infectious Diseases

AIDS

The Ivanovsky Institute of Virology, Moscow, Russia, participated with Johns Hopkins School of Hygiene, Baltimore, Maryland, in studies supported by the National Institute of Allergy and Infectious Diseases (NIAID). These investigations showed that North American strains of human immunodeficiency virus type 1 (HIV-1) found in intravenous drug users were also present in intravenous drug users in Northern Europe. Johns Hopkins School of Hygiene, the Research Institute of Pure Biochemicals, St. Petersburg, and the Ivanovsky Institute of Virology, with the National Cancer Institute (NCI), NIH, carried out a molecular epidemiology study of HIV-1 in St. Petersburg. The findings indicated that the homosexual population was infected primarily with

North American type B clades and that the heterosexual population had reactivity to A, B, C, D, and E clades, with African types predominant. The African types were introduced earlier, but the B clade has spread more rapidly.

The Johns Hopkins HIVNET (HIV Network) site has shown a remarkable increase in use of multiple condoms and a reduction in condom breakage or slippage, in Thailand in 1992–1996. Breakage with use of a single condom declined from 5.9% to 1.6% of sexual acts; use of two condoms increased from 2.8% to 49%; and breakage with use of two condoms was only 0.2%. The decline in breakage or slippage was attributable to greater expertise in condom use by commercial sex workers and clients, in response to the successful national "100% Condom Use Campaign."

Sexually Transmitted Diseases

Infection with *Chlamydia trachomatis* in the United States is primarily a sexually transmitted disease (STD), but in water-deprived tropical regions, it remains the leading cause of preventable blindness. Observations in STD clinics that a single dose of the antibiotic azithromycin cured patients infected with *Neisseria gonorrhoeae* and *C. trachomatis* has led to use of the agent for symptomatic treatment of STDs in the tropics, to reduce the burden of STDs, which increase the risk of HIV infection. A single dose of azithromycin has also been effective in curing patients with nonvenereal *C. trachomatis* infection of the eye. In efforts to avert the danger of reinfection, NIAID-supported investigators from the University of California, San Francisco, Johns Hopkins School of Medicine, Baltimore, Maryland, and the London School of Hygiene and Tropical Medicine, England, conducted community-wide treatment programs with azithromycin at sites in Egypt, the Gambia, and Tanzania. This treatment eliminated the disease. Current efforts involve assessing the feasibility and effectiveness of yearly treatment to sustain elimination of trachoma; evaluating the role of nasal carriage in persistence of the disease or reinfection; and using gene typing to carry out molecular epidemiology studies of the introduction and spread of new chlamydial strains.

Vaccines

The Swiss Serum and Vaccine Institute, Basel, is cooperating with the University of Maryland Medical School, Baltimore, and the Naval Medical Center, Callao, and the U.S. Naval Medical Research Institute Detachment, Lima, Peru, to evaluate a bivalent CVD 103-HgR/CVD 111 live oral cholera vaccine in adult volunteers in the United States and Peru. Hoffmann-La Roche, Basel, is collaborating with the University of Alabama, Birmingham, and the University of Osaka, Japan, to describe and characterize the effects of cholera toxin on the immune system.

Viral Diseases

Colorado State University, Fort Collins, has engineered resistance in *Aedes aegypti* to a West African and a South American strain of yellow fever virus.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

On September 11, 1998, an international group of researchers was brought together to discuss the current status of research and the coordination, design, and reporting of clinical trials of stem cell therapy to treat advanced rheumatic and autoimmune diseases. Such trials have been designed in Australia, Canada, Europe, and the United States to assess the safety, methods, and effect of stem cell therapy, including autologous bone marrow transplantation and therapy using peripheral blood stem cells.

The Workshop on Stem Cell Therapy for Rheumatic and Autoimmune Diseases was held at the NIH, Bethesda, Maryland, and was organized by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) with support from the Office of Rare Diseases. The Director, NIAMS, opened the meeting by acknowledging ongoing research and stressing the need to share data and research opportunities. The workshop participants agreed on the need for further discussion of four topics: (1) broad principles for study design, (2) protocol design, (3) animal models and ancillary studies, and (4) the research community. They recommended the following actions:

- creation of systematic international mechanisms and registries for sharing data;
- development of international working groups to encourage communications and planning for research on stem cell therapy; and
- formation of international subcommittees designed to develop consensus on protocols for each of the major rheumatic and autoimmune diseases.

National Cancer Institute

Breast Cancer

At the University of Melbourne, Australia, NCI is supporting the establishment of a large registry of Australian multigenerational pedigrees by collection and storage of epidemiologic information on the major recognized and putative risk factors for breast cancer and by performance of follow-up studies. This resource will be made available worldwide for research into the genetic epidemiology, biology, causes, prevention, and treatment of breast cancer. Australia is an excellent country in which to establish a Breast Cancer Family Registry. The size of the population is manageable yet sufficient for a study. Other advantages include ethnic diversity and a highly localized, relatively stable population in which families are usually intact and family members in contact with one another.

Hereditary Factors

Esophageal cancer is the seventh most common cause of cancer death worldwide. Several lines of evidence (family history, familial aggregation, segregation, and cytogenetics) suggest that genetic factors may have an important causative role in this malignant disease. Identification of susceptibility genes may allow screening of populations to identify persons at particularly high risk of esophageal cancer, a population that could then be targeted for prevention strategies (e.g., chemoprevention or early detection). Several studies are in progress or in planning to study these cancers in persons from Shanxi Province, China, where rates of esophageal cancer are among the highest in the world. Investigators have collected tumor tissue and healthy tissue from more than 200 patients. Molecular analyses of a limited number of esophageal cancer specimens are in progress.

Early Detection

NCI supports the work of investigators at Tata Memorial Hospital, Bombay, India, in a community-based, randomized-control evaluation of low-cost methods for early detection of common cancers in women. Breast and cervical cancers account for about 50% of cancer deaths in women in India. Among the diagnostic methods being evaluated are clinical breast examination without mammography, self-examination, and visual inspection of the cervix by trained female health workers. The goal is to reduce mortality by detection and diagnosis of breast and cervical cancer at an early stage. This trial is one of the first of its kind to be conducted in a developing country, and findings may be relevant to other countries and populations with limited resources (e.g., underserved populations in developed countries).

National Institute of Child Health and Human Development

The largest, most comprehensive data analysis of its kind has found that pregnant women with HIV can reduce by about 50% the risk of transmitting the virus to their infants. This reduction in risk occurs if HIV-positive women decide to deliver by cesarean section before labor begins and before the membranes have ruptured. Researchers of the National Institute of Child Health and Human Development (NICHD) analyzed data on 8,533 pairs of mothers and infants from 5 European and 10 North American studies of mother-to-infant HIV transmission. The analysis suggests a potential role for elective cesarean section as an additional intervention to decrease mother-to-infant HIV transmission, regardless of whether prophylaxis with zidovudine is received.

An NICHD-supported investigator found that, since the 1970s, infant mortality increased by more than 20% in African cities with populations between 50,000 and 1 million, while it decreased 14% in rural areas. In cities of more than 1 million population in Latin America and sub-Saharan Africa, the rate of decline in infant mortality has slowed. Poor nutrition, high morbidity due to diarrhea, low school enrollment, and rapid population growth are limiting the pace of further declines. These results underscore the need to understand trends involving population growth and urbanization of developing societies and their effect on health and mortality.

Using data from a rural population in Uganda, a study funded by grants from NICHD and NIAID provides evidence that HIV infection may lower fertility in women, both by decreasing the chances that conception will occur and by increasing rates of pregnancy loss. These findings suggest that reduced fertility among HIV-positive women could (a) result in reduced perinatal transmission of HIV; (b) produce lower estimates of HIV prevalence derived from monitoring of newborn infants; and (c) contribute to the spread of infection in societies in which failure to produce offspring may lead to dissolution of marriages and acquisition of new partners by HIV-infected women and their partners.

A new diphtheriaBtetanusBacellular pertussis vaccine was approved for manufacture and use in the United States. NICHD intramural scientists developed this vaccine. It will be produced by North American Vaccine and marketed as Certiva. Extensive vaccine trials were conducted in the United States and Sweden.

National Institute on Deafness and Other Communication Disorders

In studies funded by the National Institute on Deafness and Other Communication Disorders, scientists from countries including Belgium, Colombia, Finland, France, Germany, Israel, Japan, Norway, South Africa, and the United Kingdom, as well as scientists throughout the United States, continue their efforts to map the genes responsible for syndromic and nonsyndromic hereditary hearing impairment. Almost 40 genes on as many different chromosomes have been identified for recessive and dominant nonsyndromic hereditary hearing impairment in families from Colombia, India, Indonesia, Israel, Lebanon, Newfoundland, Pakistan, Tunisia, and the United States, including Puerto Rico. The collaborative efforts fostered by the consortium have been instrumental (a) in identifying a large number of the genes responsible for hereditary hearing impairment and (b) in advancing the understanding of these disorders.

Members of the consortium have published the sequence of a novel unconventional myosin type VIIA gene that causes Usher syndrome type 1b, the form responsible for most cases of Usher syndrome type 1. Mutations in this gene are also associated with dominant and recessive nonsyndromic hearing impairment.

National Institute of Dental Research
Intramural Research

Osteoporosis Mouse Model

During FY 98, an international research team of scientists in the Craniofacial and Skeletal Diseases Branch of the National Institute of Dental Research (NIDR) created a new animal model for studying the development of osteoporosis. The team, which included scientists from China and Italy, developed the model by disrupting the gene for biglycan, a protein that is essential for tooth and bone formation. Targeted disruption of this gene in mice resulted in offspring with normal phenotypes, as evidenced by appearance and state of health. However, as the animals aged, their skeletal structure became markedly altered. The long bones showed pronounced malformations and loss of bone density. With this model, scientists have an unprecedented opportunity for studying osteoporosis and other genetic alterations associated with bone malformation. A report of this work was published in *Nature Genetics*.

Physiological Target for Anthrax Toxin

During FY 98, an international group of scientists identified a physiological target for the lethal action of anthrax toxin. The scientists included researchers from China, Iran, and Korea, in NIDR's Oral Infection and Immunity Branch. Anthrax toxin, a biological warfare agent, is composed of three polypeptides. When injected simultaneously, two of these proteins (protective antigen and lethal factor) cause death in rodents within 1 hour. Also, exposure to components of the toxin causes disruption of macrophages in mice within 2 hours. It was already known that protective antigen is a channel-producing protein and that lethal factor is a metalloproteinase, but the physiological target for lethal factor had not been identified. The NIDR researchers helped to show that mitogen-activated protein kinase-kinase (MAPKK) is the target for the proteinase. Lethal factor causes cleavage in MAPKK, disrupting the pathway for signal transduction among cells and thereby affecting their maturation and growth. If the specific site of cleavage can be identified, agents could be developed to block the action of lethal factor. A report of this work was published in *Science*.

Office of International Health

NIDR established the Office of International Health (OIH) within the Office of the Director in March 1998. OIH, which coordinates NIDR's worldwide programs and activities, is directed by the Associate Director for International Health, who previously guided NIDR's international activities while also serving as Director, Division of Extramural Research. Now a separate office, OIH has a larger mandate. Its main functions are

- to serve as liaison with international agencies and foreign organizations;
- to coordinate dental, oral, and craniofacial research activities under agreements between the United States and other countries;
- to promote strategies to build global capacity for research on oral health; and
- to support collaborative research programs and protocols in line with NIDR's mission.

OIH also plans and implements international science exchange programs, sponsors and participates in international meetings and workshops, and disseminates research findings throughout the world. Joining the Associate Director in all these activities are the Special Expert for International Health and a new, full-time International Health Officer.

National Institute of Diabetes and Digestive and Kidney Diseases

The Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, is responsible for numerous scientific advances stemming from its international activities. These advances include the following:

- elucidation of the structure of biologically active alkaloids from amphibians, birds, and insects (specimens supplied by scientists in Argentina, Brazil, Chile, Costa Rica, Madagascar, Mexico, New Guinea, Panama, and Venezuela);
- illumination of routes and mechanisms of metabolism that lead to carcinogenic activity, as shown in studies of polycyclic aromatic hydrocarbons and their aza analogues (collaboration with researchers in Australia, Germany, and Northern Ireland);
- insights into structural modifications affecting activity at receptors for peptide, histamine, and adenosine triphosphate, as well as adenosine muscarinic and adrenergic receptors (cooperation with investigators in countries including Germany, Israel, Sweden, and the United Kingdom); and
- synthesis of a series of perfluoroalkylpyrimidines to be used as affinity labels for viral enzymes and for pyrimidine reductase (joint research with scientists in Japan).

National Institute on Drug Abuse

Canada

In a study of the Neurobiology of Relapse Induced by Stress and Drugs, the National Institute on Drug Abuse (NIDA) funded a researcher at Concordia University, Montreal, Quebec, to examine factors involved in relapse behavior of rats during reinstatement of heroin and cocaine by injection. Microdialysis will be used to assess the neuronal adaptations that may account for susceptibility to stress-induced relapse after previous long-term exposure to drugs.

A researcher at the Addiction Research Foundation, Toronto, Ontario, is exploring the roles of the cholinergic and opiatergic neurotransmitter systems in the regulation of mesolimbic dopamine neurons in drug reinforcement. Midbrain dopaminergic cells are thought to have a critical role in reward processes and to mediate many of the effects of drugs of abuse. This investigator was one of the first to successfully develop an animal model to reliably study self-administration of nicotine in rats and has already shown that nicotine activates dopamine projection neurons by mechanisms similar to those of cocaine. Two hypotheses are being tested: (1) that drug reinforcement is influenced by cholinergic projections to the ventral tegmental area from the pedunculopontine tegmental and laterodorsal tegmental nuclei and (2) that populations of μ-type opiate receptors, which are also located in the pedunculopontine nucleus, are strategically placed to modulate mesolimbic dopamine cells and to influence self-administration of cocaine.

Colombia

A prospective longitudinal study of a sample of Colombian youth (adolescents at study entry) and their parents was in its 3rd year in FY 98. Researchers at Mt. Sinai School of Medicine, New York City, New York, and Universidad de Antioquia, Medellín, are examining the causes of changes and patterns in adolescent drug use, other problem behaviors, and the consequences of drug use on the individual and his or her family. This longitudinal study is investigating interrelationships and interactions of personality, family, peers, ecological context, drug context, and cultural factors, as they affect the course of drug use, delinquency, precocious sexual behavior, and specific behaviors that increase the risk of AIDS.

Dominican Republic

In FY 98, NIDA awarded an administrative supplement to the National Development and Research Institutes, New York City, New York, and Profamilia, Santo Domingo, to conduct an exploratory qualitative study of high-risk drug users in the Dominican Republic. Drug use and HIV/AIDS are serious and growing concerns in that country. A significant number of people migrate each year from the Dominican Republic to the New York City metropolitan area and to Puerto Rico. In light of these concerns, there is a need to determine whether it is feasible to conduct cross-cultural research in the three locations, with persons from the Dominican Republic who are at high risk for HIV/AIDS. The overall goal of the project is to identify and describe populations that use heroin, cocaine, or both, particularly in terms of behaviors related to drug use and sexual activity that increase HIV risk. The aims of the study in the Dominican Republic are (1) to identify and compile information that characterizes populations using heroin, cocaine, or both; (2) to develop methods to access these populations for interviews; (3) to collect pilot qualitative data to explore determinants of HIV risk behaviors and identify patterns of travel and migration to New York City and Puerto Rico; and (4) to reinforce institutional capacity in the Dominican Republic for study of the relationship between drug abuse and HIV/AIDS. Research activities related to each of these aims are now under way, with the expectation that study results and recommendations for future research in the Dominican Republic will be available in the spring of 1999.

The Netherlands

Scientists in the Department of Medicinal Chemistry, University Centre of Pharmacy, Groningen, and the NIDA Intramural Research Program discovered a potential neural trigger for schizophrenia and a new atypical antipsychotic drug. Work also continues on the role of neuroactive steroids in drug dependence and on toxic effects related to drug abuse.

National Institute of Environmental Health Sciences

During 1998, the International Agency for Research on Cancer, supported by the National Institute of Environmental Health Sciences (NIEHS), developed several new monographs on chemical agents that have been tested for their potential to cause human cancer. In addition, a new 5-year plan for agents to be evaluated was created. NIEHS participated in the selection of these agents, which was based on information from the National Toxicology Program, bioassay results, and findings from protocols for the screening of transgenic animals and other test systems.

The proceedings of an international workshop on Alternative Testing Methodologies, which was convened by the Scientific Group on Methodologies for the Safety Evaluation of Chemicals, was published in *Environmental Health Perspectives,* in April 1998. The workshop, attended by scientists from 16 countries, was cosponsored by NIEHS; WHO's International Program on Chemical Safety; the United Nations Environment Program; the International Labour Organization; and the Scientific Committee on Problems of the Environment, of the International Council of Scientific Unions.

The purposes of the workshop were (1) to assess methods available for use as alternatives to testing large numbers of animals to predict adverse effects of chemicals in the environment on human health and (2) to identify and recommend research to fill knowledge gaps and thus lead to development of new testing methods. Workshop topics included conceptual issues, acute toxic effects, toxic effects on organs, and ecotoxicology. A joint workshop report was prepared for each topic; the report included recommendations for the development and use of alternative testing methods. Participants concluded that there are alternative testing methods and approaches that can be incorporated into tiered strategies for toxicological assessments and that use of these methods will reduce the numbers of animals required and, in some instances, reduce animal pain and distress. It was recommended that future efforts to develop test methods should emphasize procedures that reveal mechanisms of toxic effects, to provide improved prediction of adverse health consequences. Continued international cooperation was encouraged, to facilitate future progress in the development of alternative testing methods that will contribute (a) to improved protection from environmental factors that may be harmful to human health and (b) to the safeguarding of animal welfare.

National Eye Institute

Scientists in the Ophthalmic Clinical Genetics Section, Clinical Branch, of the National Eye Institute (NEI), have continued their collaboration with scientists in hospitals, clinics, and medical schools outside the United States, in successful efforts to map genes for some inherited diseases.

China

NEI is collaborating with Peking Union Medical College Hospital in conducting a survey of the prevalence of blindness and outcomes of cataract in Shunyi County, outside Beijing, and with the Zhongshan Ophthalmic Center in conducting a survey in Doumen County. These projects are similar in design and scope to a project carried out in Nepal. WHO and the Lions Clubs International Foundation are collaborating in sponsoring this work, which has led to publication of several research papers.

India

In joint efforts with scientists at the L.V. Prasad Eye Institute, Hyderabad, and the Sankara Nethralaya Hospital, Madras, India, and the Akdeniz University, Antalya, Turkey, NEI investigators continue to make important headway in efforts to map autosomal-dominant and autosomal-recessive genes for cataract. Scientists from the Ophthalmic Clinical Genetics Section are also working with investigators from the L.V. Prasad Eye Institute on productive mapping studies of autosomal-recessive genes for retinitis pigmentosa and gelatinous corneal dystrophy. In addition, studies of Bietti crystallin dystrophy and gelatinous corneal dystrophy are being carried out jointly with Juntendo University, Tokyo, Japan, and National Taiwan University Hospital, Taipei.

The Director of NEI and the Associate Director for Applications of Visual Research, NEI, have continued to work during FY 98 with physician-scientists at the Dr. Rajendra Prasad Centre for Ophthalmic Science, New Delhi. They have initiated a joint research project to develop and evaluate a questionnaire on vision function and quality of life that would be suitable for administration across subpopulations within India. The plan is to follow a research process similar to that used in the United States for development of NEI's Visual Functioning Questionnaire, including the use of patient focus groups to collect information on the variety and extent of day-to-day, vision-related problems faced by visually impaired persons.

Sweden

Many eye diseases, especially those resulting in retinal degeneration, could be successfully treated if transplantation of the human retina were possible. In animal models, transplanted visual cells do not develop and function normally. However, a new differentiating factor is being investigated by molecular biology techniques at NEI. This factor, a protein that causes neuronal-like differentiation, is being applied in vitro by NEI collaborators in Sweden at the University of Göteborg and the University of Lund, Malmö, to determine whether it will cause retinal cell differentiation. The ultimate purpose of these investigations is to develop cells that could be transplanted into the human eye and function there normally.

National Institute of General Medical Sciences

DNA–Protein Complex of *Bacillus subtilis* Bacteriophage

Scientists at the National Institute of General Medical Sciences (NIGMS) have been studying the mechanism of protein-primed DNA replication in the model bacteriophage phi29 of *Bacillus subtilis*. Health-related viruses such as adenovirus and hepatitis B virus replicate by similar protein-priming mechanisms. The long-term objective of the research is to find specific ways to interfere with viral replication.

HIV-1 gp120

NIGMS, in collaboration with the Weizmann Institute of Science, Rehovot, Israel, ascertained the three-dimensional structure of a major antigenic determinant of the HIV-1 gp120 (glycoprotein 120) bound to a fragment of the neutralizing antibody. Surprisingly, the same determinant regions from two HIV-1 isolates have significantly different structures, which may correspond to the inactive and active forms of gp120. The interconversion of these two forms may be one role of immunophilins in HIV-1 infection.

National Heart, Lung, and Blood Institute

Highlights of recent joint international activities conducted with the support of the National Heart, Lung, and Blood Institute (NHLBI) during FY 98 include the following: (a) collaboration with PAHO, WHO, and FIC in organizing the first international conference addressing the pandemic of cardiovascular disease in the Western Hemisphere; (b) partnering with South Africa in holding a joint U.S.-South African workshop on Hypertension in Blacks; (c) support for major international resources in nutrition research; and (d) planning for the G7-G8 Cardio Project with member countries. Also, as in FY 97, NHLBI is continuing its participation in the Global Initiative for Asthma.

PAHO-WHO-NHLBI-FIC Conference on the Pandemic of Cardiovascular Disease

During FY 97, the Institute initiated the planning for the first joint international conference, held in May 1998, to focus attention on the global shifts in disease burden, specifically as these trends relate to the pandemic of cardiovascular disease in the Western Hemisphere. The conference also recognized the 50th anniversaries of WHO and NHLBI. The meeting was cochaired by the Directors of PAHO, NHLBI, and FIC. It provided a forum for representatives from ministries of health and scientific leaders from the Caribbean and Central, North, and South America to discuss the costs and challenges of the shifting global burden of disease and to jointly consider opportunities for initiatives to prevent and treat cardiovascular disease in the Americas. As a direct result of this conference, NHLBI and PAHO have proposed a Pan American Hypertension Initiative. This proposal will be further discussed during a joint meeting in March 1999 of potential partners in the Americas. This initiative has the potential of affecting the health of 140 million persons with hypertension in the Western Hemisphere.

U.S.-South African Workshop Hypertension

The rapid socioeconomic changes occurring in South Africa are contributing to changes in the health of that nation, and a cardiovascular disease epidemic is imminent. The United States has faced a similar situation in the past, and NHLBI and South African officials and scientists are collaborating on the development of plans to better cope with cardiovascular disease in blacks in the United States and South Africa. A U.S.-South African Workshop on Hypertension in Blacks was hosted by NHLBI, in Bethesda, Maryland, in July 1998. Key U.S. and South African investigators pursued discussions on research topics of mutual interest and developed collaborative plans to better understand and address hypertension in black populations.

International Resources in Nutrition Research

NHLBI supports two important resources used in nutrition research in the United States, as well as in other countries. The University of Minnesota Nutrition Data System is an automated dietary interview method linked to data on the content of 92 nutrients in 16,000 brand-name food items. The system is in use, either directly or in modified versions, in several NHLBI international collaborative studies, including studies in cardiopulmonary epidemiology in China and the Intermap international blood pressure study in China, England, Japan, and the United States. NHLBI also supports the efforts of the U.S. Department of Agriculture to generate analytic data for the U.S. National Food Composition Data Base. These chemical analysis data are an international research resource, because they represent the world's largest single source of primary information on the nutrient content of foods and are used by many other countries that do not have the resources to establish their own databases.

G7-G8 International Cardio Project

Health telematics is rapidly transforming medicine. NHLBI and the National Library of Medicine (NLM) are collaborating with technical groups from G7 and G8 countries in the planning of an International Cardio Project. It is proposed that this project would use the global application of health telematics to cardiology in developing a network for use by cardiologists and physicians. The proposed aims of the project are to develop a coordinated action among member countries to share technical solutions and to prepare the way for sharing patient databases in the future.

National Human Genome Research Institute

Progress on Human Genome

An international collaborative effort is scheduled to produce the first complete, highly accurate sequence of the human genome by the end of 2003. In the United States, scientists at several sequencing centers around the country who are supported by the National Human Genome Research Institute, together with scientists supported by the U.S. Department of Energy, will sequence 60%–70% of the 3 billion base pairs in the human genome. The rest of the human genome will be sequenced at the Sanger Centre, Cambridge, England, which is funded by the Wellcome Trust, and at other sequencing centers around the world.

National Institute of Mental Health

Russia

In September 1997, the Health Committee of the U.S.-Russia Joint Commission on Economic and Technological Cooperation endorsed its joint mental health work group's recommendations for developing two program areas. These two areas include reducing disability associated with major depressive illness in primary care settings and focusing greater attention on the mental health consequences of disasters due to either natural or human causes. The continuing U.S.-Russia Joint Commission on Economic and Technologic Cooperation is now known as the Gore-Primakov Commission, formerly the Gore-Chernomyrdin Commission. The Health Committee is cochaired by the Secretary of the U.S. Department of Health and Human Services (DHHS) and the Russian Minister of Health.

Collaboration between primary health care providers and mental health specialists, to reduce disability associated with depression, was inspired by the publication of *The Global Burden of Disease* by the World Bank and WHO. In an independent assessment of the human and economic costs of disease, this groundbreaking study has helped health care professionals to refocus efforts on the consequences of disability from chronic diseases and on premature mortality. The Director of the NIH, the Director of the National Institute of Mental Health (NIMH), and the entire NIH community have taken this approach very seriously as an important dimension for planning the use of health care resources, both services and research.

With the finding that mental disorders in general and major depression in particular are leading causes of disability worldwide, the joint mental health group concluded that this public health burden could best be reduced by collaborative efforts among primary care and mental health specialists, particularly medical psychiatrists, but also psychologists, nurses, and social workers. Making the cooperation of primary care providers and mental health specialists work more effectively for the management of chronic diseases is a relatively new area of emphasis for both Russia and the United States. Such efforts need not be limited to mental health conditions.

When the U.S. members of the joint mental health work group visited Moscow in September 1997, they observed the interaction of primary care and mental health specialists in two polyclinics. Since then, Russian scientists have enlisted the support of additional polyclinics in Moscow and in Dubna, Tomsk, and Yaroslavl. Representatives from these polyclinics completed a 1-week visit to the University of Washington, Seattle, where they could observe and evaluate several model programs for initiating screening and for diagnosis and treatment of depression in primary care settings with various types of collaboration involving psychiatrists. A researcher in the university's Department of Psychiatry coordinated a discussion with colleagues from Kaiser Group Health, Puget Sound, Washington, and the Dean Clinic, Madison, Wisconsin.

After 3 days of discussions in Seattle, the Russian group developed detailed protocols for screening and confirming diagnoses, as well as two treatment models with clear criteria for monitoring symptoms, level of disability, and treatment outcome. In addition to the important funding from the U.S. Agency for International Development (USAID) to launch this project, the effort is now also supported by FIC (NIH); WHO; the World Psychiatric Association; NIMH research grantees; Eli Lilly; and Pfizer. Such diversified support is a major strength of the program as it moves into a pilot demonstration of services in FY 99.

Recent intensive evaluations of joint treatment programs compared with usual care have yielded convincing evidence that both symptoms and the number of days lost from work because of disability can be substantially reduced in the collaborative care model, by using treatment guidelines for both primary care physicians and psychiatrists. The Agency for Health Care and Policy Research and the American Psychiatric Association provide guidelines for primary care professionals and psychiatrists, respectively, for handling the more complex cases of depression. In the model, patient care is monitored by coordinators who assess the quality of care and patient outcome. This model has been used at the University of Washington for management of other chronic diseases such as diabetes, in Seattle.

During FY 98, NIMH-funded researchers in Moscow developed educational programs in Moscow, Dubna, Tomsk, and Yaroslavl, to help primary care providers to recognize depression. They worked with WHO to develop a major public education program on depression and other mental disorders in Russia. The program, entitled Nations for Mental Health, is scheduled to start in June 1999. To assist in international communication, the researchers have translated English-language textbooks on mental health into Russian. These books include the well-known Kaplan and Sadock *Manual in Clinical Psychiatry*—a project the previous Russian Minister of Health considered sufficiently important to edit herself.

After the February 1998 visit of 10 Russian psychiatrists and primary care physicians for an intensive training program at the University of Washington, Seattle, the head of the Russian delegation returned to Moscow to assemble a final protocol and initiate a pilot demonstration program on the treatment of depression at primary care sites. During a visit to Russia in the fall of 1998, two NIMH investigators and a WHO staff member evaluated the progress of the research teams in implementing the protocol. In view of the economic circumstances in Russia, the progress has been impressive. Teams have been established at five polyclinics in Moscow, two outpatient programs in Dubna, and two outpatient polyclinics in Yaroslavl. There has also been a request from a former Minister of Health to expand the program to include the city of Tomsk, and a physician from Siberia has asked to participate.

Because of the rapid development of the teams of psychiatrists, primary care physicians, and nurse coordinators, it is possible to begin the next phase of this demonstration project. The model includes the following components:

- screening for specific acute or chronic disorders;
- administration of initial therapy according to a treatment protocol, by a specialist (e.g., a psychiatrist) working closely with the primary care clinician, with long-term management by the primary care physician;
- reliance on a nurse–patient coordinator to ensure adherence to the "evidence-based" protocol; and
- measurement of change in symptoms and level of ability to function.

This model is appropriate for any chronic disease, such as hypertension, diabetes, chronic obstructive pulmonary disease, or ischemic heart disease. Implementation of the model requires programs to provide relevant education to primary care physicians and mental health specialists and joint efforts to form consensus on the treatment protocols; education of patients to encourage acceptance of treatment; and public education to change the general understanding of stigmatized disorders in particular.

Funding for some aspects of this project was provided by USAID through the DHHS Office of International and Refugee Health. WHO is also considering a related cabinet-level project on mood disorders that would use the Russian experience as a model for actually reducing disability-adjusted life years associated with one of the major disorders presented in *The Global Burden of Disease*. In addition, to help support the coordination of research for this project in Moscow, NIMH will encourage grantees to apply through FIC for funding to extend U.S. primary care research studies on mental health that include Russian investigators.

Revision of *International Classification of Impairments, Disabilities, and Handicaps*

Throughout FY 98, the International Task Force on Mental Health and Addictive, Behavioral, Cognitive, and Developmental Aspects of the *International Classification of Impairments, Disabilities, and Handicaps* (ICIDH) continued its active participation under the chair, the Assistant Director of Disability Research, Division of Services and Intervention Research, NIMH. This international task force is charged with the mental health aspects of the revision of the WHO ICIDH, which classifies the effects of disorders, traumas, and congenital anomalies in three areas:

1. the structure and function of the human body and bodily systems;
2. the purposeful activities in which people engage; and
3. the involvement of people in life situations.

The international task force members essentially completed field trials of the beta-1 version of ICIDH-2. Included in the five mandatory field trials was the translation and linguistic analysis of beta-1 ICIDH-2. The task force is responsible for translation into Russian, Tamil (Indian language), Turkish, and Yoruba (Nigerian language).

In addition to the five mandatory field trials, the task force first conducted a study to examine the cultural similarities and differences between opinions of mental health experts in Japan and the United States on ICIDH-2 items and their definitions. This study was supported by a short-term fellowship from the Japan Society for the Promotion of Science. Second, the task force performed a child's version of one of the field trials, obtaining conceptual feedback on disabilities from school-age children. Third, the task force conducted a survey of Olympic parathletes on their response to disablements as defined in ICIDH-2. Finally, the task force convened experts on the Spanish language and culture to translate ICIDH-2 into Spanish and formed a Spanish network for future participation in activities related to ICIDH-2.

Office of AIDS Research: Prevention Program

Research grants with a foreign component supported by the NIMH Office of AIDS Research have bidirectional goals: to corroborate work conducted in the United States; to extend the generalizability of research findings to other multicultural settings; and to develop new understandings of the dynamics of AIDS prevention.

NIMH supports three AIDS Research Centers that actively promote international research. For 10 years, the Center for AIDS Prevention Studies (CAPS) at the University of California, San Francisco, has supported an international program in Africa, Asia, Eastern Europe, and Latin America. Studies include the following:

- a randomized control intervention trial of an AIDS prevention program with adult night-school students in São Paulo, Brazil, resulting in a significant increase in condom use with the secondary sexual partners of young women but no increase in condom use with the primary partners;
- a feasibility study of using traditional youth organizations as a venue for AIDS prevention programs that target young persons who are in or out of school, in Bali, Indonesia; and
- a descriptive study of male adolescents living in rural areas along the Trans-African highway in Kenya who have sexual relations with resident sex workers and of female adolescents who have sexual relations with truck drivers.

CAPS is proposing 50 joint AIDS projects in which a CAPS expert in AIDS prevention would partner with an investigator in a foreign country to conduct a culturally appropriate study.

The NIMH-supported HIV Center for Clinical and Behavioral Studies at Columbia University, New York City, New York, has a history of joint research in Brazil, Puerto Rico, and South Africa. Both NIMH and FIC are contributing to efforts to build research capacity in South Africa. These efforts, which had focused on HIV and AIDS epidemiology in South Africa, have expanded to include social and behavioral science and studies in Botswana and Namibia. Joint activities include the following research:

- a study of young persons in boarding schools in Namibia, which is evaluating the effects of a manualized intervention to reduce behaviors related to HIV risk;
- a behavioral intervention study of men and women seeking care in STD clinics in Durban, Kwazulu, Natal, South Africa; and
- testing of a program for culturally oriented prevention of STD in migrant laborers in Kwazulu, to determine the effects on HIV and STD incidence.

The Center for AIDS Intervention Research, Milwaukee, Wisconsin, has recently begun collaborative studies in St. Petersburg, Russia. The research team has identified an alarming prevalence of STDs and HIV among young persons, and prevention programs are being planned.

National Institute of Neurological Disorders and Stroke

Discovery of Gene for Two Types of Muscular Dystrophy

An international research effort supported by the National Institute of Neurological Disorders and Stroke (NINDS) has yielded the discovery of a gene that, when mutated, causes two types of muscular dystrophy. The gene, found on chromosome 2, codes for a newly discovered protein called dysferlin, which is produced by skeletal muscles. Mutant dysferlin was seen in several families in which members had either Miyoshi myopathy, a very rare muscle disorder, or one form of limb-girdle muscular dystrophy, a more common condition. Dysferlin may be involved in maintaining the membranes of structures within cells that perform functions critical to cellular activity. Included in the research team were investigators from the Research Institute, Montreal General Hospital, Quebec; Hôpital de la Salpétriére, Paris, France; the University of Padua, Italy; the National Institute of Neuroscience, Tokyo, Japan; King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; Hospital Sant Pau, Barcelona, Spain; and La Rabta, Tunis, Tunisia.

Neural Stem and Progenitor Cells in Adult Brain: Strategy for Repair

One of the reasons there is little recovery from damage to the central nervous system resides in the inability of the adult brain to replace neurons lost to injury or disease. The degree of recovery that is possible arises from synaptic and functional plasticity rather than the restoration of lost neurons. In recent studies, several NINDS grantees collaborated with scientists from Osaka University, Japan; the Institute of Biomedical Investigation, Mexico City, Mexico; and the University of Valencia, Spain. The research team demonstrated the presence of neuronal precursors within the subventricular zone in the brains of adult birds, rodents, and humans. In vivo, these precursors produce neurons that are recruited to restricted regions, such as the avian neostriatum and the mammalian olfactory bulb. Neural stem cells, which are the self-renewing precursors of neurons and glia, have been isolated from the central nervous systems of embryonic, adult, and aged mammals and have been maintained in culture for months. Although the size of the pool of precursor cells is minimally reduced with age, explants of these cells, taken from hosts of different ages, display identical properties and responsiveness to neurotrophic factors. Thus, neuronal precursors in the brain persist into senescence. Understanding the potential of these neurogenic cells, both in vivo and in vitro, will be critical in determining how best to use them to meet the challenge of repairing the damaged nervous system.

New Clues About Fatal Childhood Disease, Ataxia-Telangiectasia

For the first time, scientists have shown conclusively how the protein that is missing or altered in the fatal childhood disease ataxia-telangiectasia (AT) acts as a key regulator of cell division after DNA damage. The finding helps researchers to understand how cells form tumors in patients with AT, and it may lead to new understanding of other neurological and immune disorders. The new research shows that the ATM (AT mutated) protein is a protein kinase that reacts to DNA damage by chemically modifying and triggering accumulation of a molecular "brake," p53 protein. This tumor-suppressor protein, which is the master control switch for a process that normally prevents cells from dividing, is defective in about one-half of all human cancers. In patients with AT, the ATM protein is missing or defective. Consequently, the accumulation of p53 is delayed, allowing cells to replicate without repair of DNA and thereby increasing the risk of cancer. The ATM gene was isolated in 1995 at Tel Aviv University, Israel, with collaboration from an international team partially supported by NINDS. Until now, however, researchers have been uncertain about precisely how the protein produced by this gene works. The new finding was reported by the investigator from Tel Aviv University, who continues to receive support from NINDS. Now that scientists better understand how the ATM protein works, they can move toward the next stage of research—designing new treatments for AT and possibly for cancer and other disorders.

National Institute of Nursing Research

Extramural Grants

A grantee supported by the National Institute of Nursing Research (NINR) is conducting field research in Matlab, Bangladesh, on a public health intervention to prevent or reduce the incidence of cholera in areas where people must depend on natural groundwater after natural disasters such as flooding. The research involves a simple filtration method that uses widely available sari cloth to filter household water. The intervention is based on earlier studies that found sari cloth effective in reducing the number of plankton associated with *Vibrio cholerae* in surface water to below the infectious level that causes cholera. Investigators are evaluating the effective use of the technique by villagers, including whether the number of *V. cholerae* cells in water and the incidence of cholera are reduced.

Another NINR grant involves a 10-site, randomized control study in Canada and the United States. The research is designed to reduce the unacceptably high rates of birth by cesarean section in these two countries. Earlier studies conducted on a smaller scale showed that the amount of "labor support" by caregivers during active labor can influence cesarean delivery rates and other adverse events related to childbirth. The elements of labor support being studied include companionship, attention to emotional needs, and comfort. The researchers are evaluating the results of two types of nursing care on women in labor—continuous support and the usual intermittent nursing care. They are comparing the effects of these types of care on rates of cesarean delivery and forceps delivery and requirements for pain reduction, particularly for administration of epidural anesthesia. Cost-effectiveness is also being addressed. The findings will contribute knowledge about the effectiveness of labor support for a variety of events related to childbirth, such as prolonged hospital stay and postpartum depression. The results of this study are expected to inform policy decisions about the staffing of hospital delivery suites.

NINR funds U.S. training fellowships for three predoctoral students who are performing dissertation research in Nicaragua and Peru. The trainees are undertaking studies on the relationship between the women's movement and women's health in Nicaragua; understanding and management of cancer in Peruvian Amazonia; and improving infant nutrition in Trujillo, Peru.

International Meetings

NINR staff participated in the meeting of the International HIV Nursing Research Network, in London, England. The network participants meet twice a year to collaborate on international research on the care of patients with HIV.

NINR also hosted a Visiting Scholar, who is the Chair of Acute Care Nursing at Cabrini Hospital, Deakin University, Victoria, Australia. She was briefed about U.S. nursing research on patient outcomes and about enhancing the educational and research activities of her institution.

National Library of Medicine

Internet Connectivity at Malaria Research Sites in Africa

"What a pleasure for us and our collaborators to sit in our offices and browse the Web sites, being in contact with the world in a few seconds, looking for the hidden world. What a great potential we are discovering." These words of the Director of the Malaria Research and Training Center, Bamako, Mali, reveal at once the excitement of African scientists and the potential that Internet access holds for scientific research. Since June 1998, he and his colleagues at the Center have had access to the Internet and the World Wide Web through microwave technology. The equipment (including a local network), installation, and training were funded by NIAID; NLM; the Office of the Director, NIH; and the World Bank.

This story from Mali is the first chapter in the work of the Multilateral Initiative on Malaria (MIM) Communications Working Group, chaired by NLM. The major objectives of MIM are support for African scientists, the ability of malaria researchers to connect with one another and sources of information, and the creation of new collaborations and partnerships.

The initial meeting of the MIM Communications Working Group was held at NLM, in Bethesda, Maryland, in January 1998. In attendance were malaria research scientists, health information professionals, telecommunications experts, and representatives of the major agencies that fund MIM. In keeping with the goal of supporting a broad spectrum of basic and operational needs for malaria research, the investigators requested communications and connectivity capabilities sufficient to provide robust and reliable electronic mail (e-mail); links among research sites; access to the full text of journal articles; database searching; exchange of large files and mapping data; and timely access to electronic information resources worldwide.

In addition to the malaria research site in Mali, the MIM Communications Working Group endorsed five other locations for the initial connectivity phase: the site of the Centers for Disease Control and Prevention (United States) and the Kenya Medical Research Institute (KEMRI), in Kisian; the site of the Wellcome Trust (United Kingdom) and KEMRI, in Kilifi; and three sites of the National Institute of Medical Research, in Dar es Salaam, Ifakara, and Amani, Tanzania. Several of the sites already have computer equipment and training. Most of the sites are in relatively remote locations, however, and traditional means of connecting to the Internet are not viable, because of the unreliability of telephone service or restrictions on the bandwidth of rates for data transfer.

Subsequently, NLM supported site visits and assessments, consultation, and evaluation and testing of equipment existing at the site. In drafting an implementation plan, the MIM Communications Working Group considered issues such as user training, in-country licensure of technology, and allowances for future technological advances (e.g., predicted worldwide availability of low-cost commercial satellite systems).

The plan recommends immediate use of affordable technologies to provide high-speed and reliable information and communication links. The goal is to achieve timely improvement in the ability of scientists to collaborate in research and to disseminate the findings. Recommended technologies are VSAT, which uses a geostationary satellite and a small earth station, and microwave, which uses radio waves. Microwave equipment is less expensive but is limited to line-of-sight transmission. The MIM sites that request a radio or VSAT link must gain permission from the relevant in-country authority.

With the Mali model fully operational, NLM has stepped forward with an offer to fund the initial equipment and installation costs at these five sites if partner funding organizations make a commitment to support ongoing operational costs. Sustainability is an essential ingredient for achievement of lasting connectivity at these research sites. At the site in Kisian, Kenya, a funding partnership between NLM and the Centers for Disease Control and Prevention is firmly in place. An NLM special expert is responsible for project coordination.

National Center for Research Resources

The National Center for Research Resources supports the Cambridge Crystallographic Data Centre, England, which builds and maintains the Cambridge Structural Database, the largest searchable database of crystal structures that have been determined by biomedical researchers. This database contains crystal structure information for more than 190,000 organic and metal organic compounds and is the only available file of x-ray crystallographic coordinates for compounds of low molecular weight. The Cambridge Crystallographic Data Centre distributes the database and software to more than 600 academic and commercial users worldwide.

Center for Information Technology

The Computational Bioscience and Engineering Laboratory (CBEL) of the Center for Information Technology (CIT) collaborated with a Visiting Scientist from Israel in investigating new techniques related to Doppler ultrasound imaging of cardiac function. This effort, entitled Method and System for Doppler Ultrasound Measurement of Blood Flow, resulted in the award of a U.S. patent to the NIH on December 30, 1997. The patent describes a method for providing Doppler data corrected for misalignment between the direction of flow within a vessel and the beam orientation of an ultrasound probe. In addition, the patent describes a new system for measuring and recording experiment time and free space position and orientation of an ultrasound probe. This method has been added to a conventional ultrasonic Doppler color flow mapping system. From the identified flow direction and the information on orientation and position for each acquired two-dimensional ultrasound image slice, the two-dimensional Doppler signals are appropriately transformed into corrected velocity values. These values can then be used to construct a three-dimensional flow field as a function of time. This method may be shown to extend the diagnostic quality and range of this technology.

In early 1998, representatives of the Radiation Effects Research Foundation, a joint Japanese-U.S. research organization studying radiation-related health effects of the Hiroshima and Nagasaki atomic bombings, toured several prominent U.S. research centers, including the NIH. Two staff members of the foundation's Department of Information Technology visited CIT, where they were given an overview of CIT's Office of Computational Bioscience and demonstrations of services provided by the Scientific Computing Resource Center, the Center for Molecular Modeling, and the Radiology Consultation WorkStation (RCWS) project at NCI's Radiation Oncology Branch in the Warren Grant Magnuson Clinical Center.

In April 1998, the U.S. Information Agency's *Voice of America* sponsored a 3-day seminar on Broadcasting Health, which was related to electronic media programs dealing with children's health. In their visit to the NIH, 30 participants from radio stations in Africa, Asia, the Caribbean, and Latin America received a CIT presentation on Telemedicine—Medical Advice and Patient Treatment via Live Video, including a demonstration of RCWS, which was developed by staff of CBEL. CIT demonstrated the potential that the high-speed RCWS environment can provide for effective communication between geographically distant locations. Using the RCWS system, which is based on asynchronous transfer mode networking technology, a simulated medical teleconference was conducted between two buildings on the NIH campus, Bethesda, Maryland.

During FY 98, a Special Volunteer who is a senior scientist from the Karpov Institute of Physical Chemistry, Moscow, Russia, worked in CIT's Mathematical and Statistical Computing Laboratory (MSCL). He developed theoretical and computer-oriented techniques for calculating conformational and environmental effects on the dynamic behavior of chemical reactions in biologically important systems. In September 1998, another scientist from the Karpov Institute of Physical Chemistry joined MSCL researchers to extend the research on this project. The Special Volunteer also assisted MSCL researchers in preparing a monograph on the theory of rate processes as applied to certain identified chemical reactions. In addition, he has made many important contributions in the application of Kramer's model for calculating reaction rates.

Center for Scientific Review

Country-to-Country Activities and Bilateral Agreements

The Center for Scientific Review (CSR) was represented in a delegation of NIH representatives and representatives from the U.S. Department of Energy, the National Science Foundation, the U.S. Department of Agriculture, the U.S. Department of State, and the U.S. Geological Survey. The delegation participated in workshops in Prague, Budapest, and Piestany to discuss U.S. international grant programs with scientists and officials of the Czech Republic, Hungary, and Slovakia, respectively. One intent was to provide information on grant support to scientists in these countries. The workshops provided the opportunity to discuss the grant process with foreign scientists and to make suggestions for preparation of more competitive grant proposals.

The Director currently in charge of the review and evaluation of research at the Chinese National Academy of Sciences spent 6 months at the NIH on a visit that was hosted and organized by CSR staff. She visited NIH extramural programs in many of the Institutes and at George Washington University, Washington, D.C., and attended study section meetings to observe reviews of grant applications.

In FY 98, CSR hosted two delegations of scientists from China representing engineering and physical and health sciences and many international visitors who came to study the referral and peer review procedures and recent innovations that have been introduced to improve, expedite, and streamline the processes. These visitors were from Armenia, England, Germany, Japan, Russia, Saudi Arabia, Sweden, and Taiwan.

Warren Grant Magnuson Clinical Center

The Warren Grant Magnuson Clinical Center participated in a variety of international activities during FY 98. Staff presented research findings at numerous international conferences on subjects such as stem cell transplantation and cytokines; brain tumors and spinal imaging; use of magnetic resonance imaging in multiple sclerosis; risk factors from low doses of ionizing radiation; disability in arthritic conditions; and intervention through occupational therapy in dementia.

Staff was also involved with the formulation and distribution of investigational medications and collaboration with international researchers in diverse fields of clinical investigation.

II.

Office of the Director National Institutes of Health

INTRODUCTION

The Director of the National Institutes of Health (NIH) provides overall leadership for NIH activities. He maintains close liaison with the Office of the Secretary, U.S. Department of Health and Human Services (DHHS), in matters relating to medical research, research training, education and training in the health professions, human resources, and biomedical communications. The Director also works closely with other DHHS officials to coordinate programs.

The Office of the Director comprises the following positions: a Deputy Director; Deputy Directors for Extramural Research, Intramural Research, and Management; and Associate Directors for Intramural Affairs, Administration, AIDS (acquired immunodeficiency syndrome) Research, Communications, Disease Prevention, Science Policy and Technology Transfer, Legislative Policy Analysis and Development, Research on Minority Health, Research on Women's Health, Alternative Medicine, and Behavioral and Social Science Research.

NIH Director Dr. Harold Varmus and members of his staff represent the NIH by participating in meetings with officials of foreign governments and in international conferences. During fiscal year 1998 (FY 98), the Director participated in several international meetings, including the Annual Meeting of the World Economic Forum, in Davos, Switzerland, on January 28–February 1, 1998.

OFFICE OF AIDS RESEARCH

The Office of AIDS Research (OAR) is responsible for coordinating NIH intramural and extramural research efforts and related activities relevant to AIDS and the human immunodeficiency virus (HIV), which causes AIDS. For international activities related to AIDS research, OAR collaborates with the NIH Institutes and Centers that support and conduct such research, other organizations in the U.S. Public Health Service and DHHS, and other governmental and nongovernmental organizations. Specific efforts are described in the chapters for the individual Institutes and Centers.

OAR supports activities that (a) will help to stimulate collaborative AIDS-related research efforts between U.S. investigators and investigators in other countries and (b) will facilitate access by foreign investigators and care providers to state-of-the-science technical information and information about the clinical management of HIV-infected patients. In addition, OAR meets with delegations and individual scientists, officials, and program staff working in AIDS-related prevention programs in other countries, to facilitate a broad understanding of the NIH AIDS-related research programs.

Highlights of International Activities

OAR continues to support forums for researchers, scientists, and health care administrators in developed and developing countries to meet and exchange information. OAR provided support for the Workshop on International HIV/AIDS Prevention Research Opportunities, which was held in San Francisco, California, on April 17–20, 1998, for the purpose of bringing together scientists and health care administrators from developed and developing countries to discuss country-specific agendas for comprehensive HIV prevention and for development of strategies for preventive intervention.

The 10th joint meeting of the AIDS Panels of the U.S.-Japan Cooperative Medical Science Program was held in Williamsburg, Virginia, on March 18–20, 1998. The purpose of these yearly meetings is to enhance collaborations between the U.S. and Japanese colleagues. The meeting focused on AIDS vaccine research to further efforts related to the 1997 Denver (Colorado) Summit Declaration on HIV Vaccines. Panels at the annual meeting exchanged scientific information on HIV/AIDS research activities.

Summary of International Programs and Activities

Extramural Programs

OAR does not award grants or contracts in direct support of specific AIDS research projects, but OAR discretionary funds may be provided to individual NIH Institutes and Centers that identify promising opportunities or critical research needs. In FY 98, such funds were provided to the Fogarty International Center in support of collaborative research on prevention of HIV infection through the AIDS International Training and Research Program. These funds will support awards to domestic institutions for training of predoctoral and postdoctoral researchers, including medical students and residents (Table II-1). This initiative will provide international training opportunities and support ongoing AIDS research in the participating countries. It may also facilitate future international collaborative research.

The HIV epidemic has become more severe and is rapidly increasing among women of childbearing age in developing countries. To address this problem, OAR provided discretionary funds to NIH Institutes and Centers in support of research on early detection, counseling, and prevention of HIV infection for pregnant women in four developing countries: Brazil, South Africa, Uganda, and Zimbabwe.

Support was provided for two studies in Rio de Janeiro, Brazil. One study will be conducted by collaborating investigators at the University of California, Los Angeles, and at hospitals in Brazil, to study rapid testing for early identification of HIV infection in pregnant women and to provide early perinatal intervention. The other collaborative study will be conducted by investigators at the University of Maryland, Baltimore, and in Brazil, to study rapid HIV testing in pregnant women, at entry into the medical care system and late in pregnancy. The purpose of this study is to determine whether early identification of maternal HIV status will fa-

TABLE II–1.

Initiative by Office of AIDS Research and Fogarty International Center To Train New and Minority AIDS Researchers and Recipients of Support

Principal Investigators	AIDS International Training and Research Program Centers	Collaborating Countries
Lee H. Harrison	University of Pittsburgh, Pennsylvania	Brazil
Carlos Del Rio	Emory University, Atlanta, Georgia	Georgia, Mexico, and Vietnam
William A. Blattner	University of Maryland, Baltimore	Brazil and West Indies (including Barbados, Jamaica, and Trinidad and Tobago)

cilitate more timely follow-up and initiation of therapy for both mother and infant.

A site for the HIV Network for Prevention Trials in Durban, South Africa, received supplementary funds for a pilot project to implement voluntary counseling and testing for women, with follow-up through the maternity public health clinics. In addition, Johns Hopkins University, Baltimore, Maryland, received funds for two studies. In a study of mothers and infants in Uganda, investigators are analyzing HIV outcomes in infants born to HIV-infected women, in relation to whether the mother received treatment for sexually transmitted diseases (STDs) during pregnancy. The other study will help to develop strategies to improve implementation of treatment and breastfeeding guidelines for HIV-infected pregnant women in Uganda. Also, Stanford University, California, was provided funds for a pilot study in collaboration with investigators in Harare, Zimbabwe. The researchers will assess the relationship between coinfection with human papillomavirus in the genital tract of HIV-infected pregnant women and risk of transmission of HIV from mother to infant.

Injection drug use has increased among the Mexican population, especially school-age children. In addition, issues related to the border between the United States and Mexico are a focus for collaboration between the two countries. OAR provided funds for a collaborative initiative of the University of Texas, San Antonio, to study the injection drug use and high-risk sexual behavior in El Paso, Texas, and Ciudad Juárez, Chihuahua, Mexico, which are cities on the U.S.-Mexican border.

International Meetings

OAR cosponsored a Workshop on Research Opportunities in AIDS and Other Infectious Diseases in the Former Soviet Union. This workshop provided an opportunity for scientists, health care providers, and community advocates to collaborate on current HIV/AIDS issues in the Newly Independent States of the Former Soviet Union. Other OAR-supported conferences and workshops were the Worldwide Development and Challenges in HIV/AIDS Conference, in collaboration with the Royal Society of Medicine, in London, England, on March 30–April 1, 1998; the 2nd International Summit on Correlates of Protective Immunity to HIV Infection and Disease, in London, in May 1998; and the XIIth International Conference on AIDS, in Geneva, Switzerland, on June 28–July 3, 1998. In addition, OAR provided support for the 2nd International Symposium on HIV Prevention, an official satellite meeting at the XIIth World AIDS Conference. This symposium, cosponsored by a range of U.S. and international organizations, highlighted HIV prevention science, practice, and policy, through plenary addresses. Concurrent sessions were devoted to behavioral and biomedical strategies for HIV prevention.

OFFICE OF RESEARCH ON WOMEN'S HEALTH

The Office of Research on Women's Health (ORWH) was established in September 1990 within the Office of the Director of the NIH, to serve as the focal point for NIH research on women's health. The Office has the following mandate:

- to strengthen, develop, and increase research into diseases, disorders, and conditions that affect women and to determine gaps in knowledge about such conditions and diseases;
- to ensure that women are appropriately represented in biomedical and biobehavioral research studies, especially in clinical trials supported by the NIH; and
- to develop opportunities and support for recruitment, retention, reentry, and advancement of women in biomedical careers.

ORWH works in partnership with the NIH Institutes and Centers to ensure that research on women's health is an integral part of the scientific fabric at the NIH and throughout the scientific community.

Research on women's health is a global concern, and ORWH has worked with investigators, health care providers, and women's health advocates around the world on studies and activities to improve the health of women. ORWH has cosponsored international conferences, and staff members have made presentations at scientific meetings abroad and collaborated with colleagues visiting from other countries.

ORWH continues to be involved in the implementation of the Platform for Action developed at the United Nations 4th World Conference on Women, in Beijing, China, in September 1995, and is at the forefront of other international women's health initiatives. The Office compiles up-to-date information on women's health research by canvassing members of the NIH-wide Coordinating Committee on Research on Women's Health for information on current studies and research activities. Most recently, ORWH provided updates for the women's health research portion of the DHHS document entitled Implementing Cairo, a symposium to address the conditions of women worldwide.

ORWH collaborated with the Public Health Service's Office on Women's Health in sponsoring the international teleconferences from Adventures in Health, Education, and Agricultural Development, Inc. These teleconferences facilitate information exchange between women throughout Africa, the Caribbean, and the United States, to develop strategies for resolving problems that confront women around the world. Healthy Behaviors, the first of four teleconferences, was held at Howard University, Washington, D.C., on March 25, 1998. Experts in the field of women's health addressed issues such as infectious diseases, reproductive health, HIV/AIDS, STDs, prevention of violence, harmful practices, and the mature woman (Beyond the Childbearing Years).

In May 1998, ORWH cosponsored a women's health conference on Occupation, Cancer, and Reproduction, which was held in Reykjavik, Iceland. The focus of the meeting was elucidation of possible links among occupation, cancer, and reproductive problems in women. This meeting addressed gender-related differences in the causes of cancers of the breast, ovaries, stomach, lungs, kidneys, central nervous system, and bladder, as well as renal cell carcinoma, hematolymphopoietic malignant disorders, glioma, and sinonasal cancer. Gender-related differences in risk factors for cancer were also explored. These differences included gender-specific occupational hazards, including exposure to organic solvents in dry-cleaning businesses and hair salons and the risks faced by female personnel in medical science and technology and by female workers in the industries that process wood, paper, asbestos, silica, nickel alloy, and vitreous fiber. Specific environmental risk "pockets" were examined, including populations in Italy, Norway, Poland, Sweden, and the United Kingdom.

In June 1998, ORWH was involved in several international activities. The Associate Director for Research on Women's Health (Director, ORWH) was a keynote speaker at the 3rd International Symposium: Women's Health and Menopause Risk Reduction Strategies—Improved Quality of Health, at the invitation of the Giovanni Lorenzini Medical Science Foundation, in Florence, Italy. She made a presentation entitled Women's Health and Menopause: Epidemiology—the USA Experience; provided information about the cardiovascular status of women in the United States; and contributed to discussions of menopause, hormone deficiency, hormone replacement therapy, and cardiovascular research on women. Also in June, the ORWH Director was a keynote speaker at the International Women's Leadership Conference, in Nice, France. She focused on three areas relating to women in academia: education, research, and women's health, with special emphasis on the research agenda for women's oral health for the 21st century. Through the National Institute of Dental Research, ORWH cosponsored the conference, which included presentations in the following areas:

- preparation of women for advancement to senior administrative roles;
- examination of international advancement of women in academia and research;
- issues related to entry and reentry in careers in academics and research;
- emerging issues in women's oral health and research and incorporation of these issues into curricula; and
- advancement of the needs of junior faculty.

Also in June, the ORWH Director greeted the Duchess of York during her visit to the NIH and reviewed with her the NIH-supported goals of improving the health of women through research. ORWH facilitated a meeting of representatives of the NIH Institutes and Centers and ORWH staff with Dame Rennie Fritchie and colleagues from Gloucestershire, England, and Belfast, Ireland, to discuss the Pennell Initiative for Women's Health. That report outlines findings and recommendations for positive steps to a better and healthier later life for British women, by raising awareness of issues affecting the health of women from menopause to old age. The recommendations include detection and treatment of cancer, coronary heart disease, bone and joint disorders (e.g., arthritis and osteoporosis), and depression. One important finding is that isolation in the very elderly can lead to serious physical and emotional problems. Another is the need for women to take a multidimensional view of their health, by blending a range of holistic, alternative, and traditional approaches. Discussions were conducted to share information about similar initiatives funded by the NIH.

The Medical Advisor to the Director, ORWH, spoke at the June 1998 symposium on Research Advances in Medicine: The Effects of Perinatal Exposure to Cocaine. The symposium was held at the 151st annual meeting of the American Psychiatric Association, in Toronto, Ontario. The Medical Advisor made a presentation entitled Perinatal Cocaine Exposure Is a Persistent Phenomenon: What Can We Do to Make a Difference? In addition, the Medical Advisor was a keynote speaker on the mental health needs of women, at the 2nd Congress on Psychiatric Diseases in Women, Section on Women's Mental Health of the World Psychiatric Association. The congress was sponsored by the Department of General Psychiatry, University of Vienna, Austria. The Medical Advisor gave an overview and described practical guidelines on addiction in women and chaired a session on addiction and mental health.

In July 1998, the ORWH Director and Acting Deputy Director met with the Secretariat of Health of Mexico, who visited the NIH to discuss the U.S.-Mexico Binational Commission's Health Working Group, which is part of the Women's Health and Reproductive Health Core Group. In August 1998, ORWH was among the sponsors of the Pregnancy and Rheumatic Diseases Conference, in Trondheim, Norway. This international conference had the following goals:

- to describe rheumatic diseases related to pregnancy in terms of the biology of pregnancy;
- to present new findings on the biology of specific problems with well-studied pathogenesis (e.g., neonatal lupus and anti–phospholipid antibody);
- to define consensus measurement criteria for fetal and maternal outcomes, by focusing on the science of clinical measurements during pregnancy and on the development of consensus answers to questions relating to the whole patient—simultaneous measurement of disease activity and pregnancy complications, the biology of preeclampsia in rheumatic disease, and short- and long-term fetal outcomes;
- to pose questions about pregnancy in the context of the biology of gender, by presenting new information on gender that is largely published in the literature of molecular genetics and endocrinology, to introduce the relevance of this topic to the study of pregnancy with pathological complications;
- to present a forum for discussion of important clinical topics; and
- to develop new directions for research.

In September 1998, through the National Cancer Institute (NCI), ORWH supported the 3rd International Symposium on Hormonal Carcinogenesis, in Seattle, Washington. The meeting brought together a group of epidemiologists, basic scientists, and clinicians of widely diverse disciplines, including cell and molecular biology, endocrinology, biochemistry, reproductive toxicology, pathology, gynecologic medicine, and epidemiology. These symposia provide an international forum for researchers studying the role of hormones and other growth regulators in the initiation, promotion, and progression of hormone-associated cancers.

ORWH also supported the U.S.-Mexico Border Conference on Women's Health, which was held on South Padre Island, Texas, in September 1995, and assisted in the development of proceedings covering a range of topics and diseases, including the following: breast, ovarian, and cervical cancers; smoking in Latinas; mental health in Latinas; HIV/AIDS in Hispanic populations; STDs in adolescents; teen pregnancy; contraceptive technologies; prenatal care; occupational health hazards; public outreach; diabetes; domestic violence; and barriers to health care.

Also in September 1998, the ORWH Director provided a keynote address at the meeting of the North American Menopause Society, in Toronto. She presented an overview of the changing scientific model in the 21st century, to include the causes, progression, and treatment of conditions and diseases that affect women; the emergence of women's health issues; and the role of ORWH in defining an agenda for research on women's health, with emphasis on recommendations for research on menopause.

OFFICE OF RESEARCH ON MINORITY HEALTH

The Office of Research on Minority Health (ORMH) was established within the Office of the Director of the NIH, to serve as the focal point for NIH research on eliminating health disparities in minority populations. ORMH has a twofold mission: (1) extending healthy life and reducing the burden of illness among minorities through targeted research and (2) expanding the participation of underrepresented minorities in all phases of biomedical and behavioral research. At all stages of life, the minority groups in the United States have poorer health and higher rates of premature death than the majority groups. There are adequate data to explain why minority populations have the highest prevalence of diseases such as asthma and AIDS. Less is known, however, about how to reduce the disproportionate burden of these illnesses, and it is still unclear why other health conditions, such as lupus and certain cancers, affect minorities disproportionately.

ORMH uses two mechanisms to accomplish its mission: the ORMH budget and the Minority Health Initiative (MHI). To identify gaps where special initiatives are needed to address disparities in health, ORMH also uses a consultative approach. Accordingly, the priority-setting process is informed through extensive consultations with minority educators, the NIH Institutes and Centers, research scientists, and members of grassroots community organizations. Because ORMH is not authorized to award grants, the Office addresses identified gaps in health research and training by sponsoring or cosponsoring pilot initiatives through partnerships with the NIH Institutes and Centers.

MHI is a comprehensive program administered by ORMH and implemented in collaboration with the NIH Institutes and Centers. The program focuses on developing and testing interventions that will reduce the disproportionate burden of disease among minority populations and on designing successful strategies to promote healthy behaviors across the life span. The program also focuses on developing MHI sponsors or cosponsors and on supporting research training initiatives, to ensure the representation of minorities in careers related to health research.

Consistent with the NIH emphasis on international as well as domestic disparities in health, MHI supports international research and research training projects aimed at decreasing health disparities. For example, under the rubric of MHI, ORMH, and the National Institute of Allergy and Infectious Diseases (NIAID), ORMH cosponsored an initiative in Africa to decipher the genetic code of the malarial parasite *Plasmodium falciparum*. There has been a dramatic resurgence of malaria in the world's tropical regions, and deciphering the genetic code of the malarial parasite is part of a broad-based NIH strategy to control this mosquito-borne disease and other diseases that threaten global health. The World Health Organization (WHO) estimated that malaria-related deaths worldwide in 1992 numbered between 1.5 and 3 million. In 1995, approximately 1,200 cases of malaria were reported in the United States. Although most of these cases were in persons who had been infected while traveling abroad, local transmission has been documented in California, Florida, Michigan, New Jersey, New York, and Texas in recent years.

ORMH also supports the MHI-sponsored Minority Training Program in Tropical Medicine, at the Malaria Research and Training Center, University of Mali, Bamako, through a partnership with NIAID and the University of Maryland, Baltimore. The research training initiative in Mali provides U.S. minority investigators and other U.S. investigators with international research training experiences in emerging infectious diseases. In concert with the overall NIH malaria initiative, through its partnership with NIH's Fogarty International Center, and through MHI, ORMH supported the International Conference on Malaria, in Dakar, Senegal, in January 1997. This meeting served as a forum for the international research community to develop an agenda for malaria research and training and identified potential funding sources for scientists from areas where malaria is endemic.

OFFICE OF DISEASE PREVENTION

Office of Dietary Supplements

The Office of Dietary Supplements (ODS) was established by the Dietary Supplement Health and Education Act of 1994 (Public Law 103-417), which amended the Federal Food, Drug, and Cosmetic Act "to establish standards with respect to dietary supplements." ODS was organized within the Office of the Director, NIH. Formal operations began in November 1995, with the mission of strengthening knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public, to foster an enhanced quality of life and health for the U.S. population.

In FY 98, ODS participated in several international workshops and a conference.

The meeting entitled The Path to Maternal and Child Health: the PVO Role in Improving Iron and Vitamin A Status was organized by the Child Survival Collaborations and Resources Group, a consortium of private voluntary organizations (PVOs) supported by the U.S. Agency for International Development (USAID). This conference attracted representatives from 80 organizations, including managers of micronutrient programs in Africa, Latin America, Southeast Asia, and Russia. ODS supported the participation of three Russian clinicians and three Russian PVO program managers in the workshop, to build on U.S.-Russian collaboration in the area of micronutrient malnutrition. Goals of this research are to identify more precisely the nutritional status of the U.S. and Russian populations; to focus on areas where more research is needed; to develop and implement appropriate and sustainable interventions; and to perform regular surveillance to assess the effectiveness, safety, and quality of such interventions. The workshop served as a forum for the exchange of current knowledge on the epidemiologic profile of iron deficiency and intervention practices in the Russian Federation and for further definition of plans for joint efforts to alleviate this serious deficiency.

ODS cosponsored an international conference on the Nutritional and Health Benefits of Inulin and Oligofructose, in Bethesda, Maryland, on May 18–19, 1998. The meeting was designed to review and assess the current scientific evidence on the health benefits and physiological functions of inulin and oligofructose, which are polymers of fructose that function in the storage of carbohydrates in plants. These compounds are not digestible by humans; they have properties similar to those of dietary fiber. Topics at the conference included the effects of inulin and oligofructose on intestinal microflora, lipid metabolism, immunity, and risk of breast and colon cancer. This meeting was cosponsored with the American Dietetic Association; the American Society for Clinical Nutrition, Inc.; the American Society for Nutrition Sciences; the Canadian Society for Nutritional Sciences; the Institutes of Food Technologists; ORAFTI; the Department of Nutrition, Pennsylvania State University, State College; and the Agricultural Research Service, U.S. Department of Agriculture (USDA). The proceedings of this workshop are scheduled to be published in the *Journal of Nutrition,* in June 1999.

A workshop on The Problem of Overcoming Selenium Deficiency in the Russian Federation was held in Moscow and Tyumen, Russia, on June 16–19, 1998. Aims of this workshop were to exchange recent research findings on selenium deficiency and dietary supplementation; to obtain detailed information on the adequacy of dietary intake of selenium in the population of the Russian Federation; and to discuss the intervention approaches of other countries for alleviating selenium deficiencies, including supplementation with selenium with high bioavailability (e.g., fortified yeast). Another objective of the meeting was to bring together current research findings on the role of selenium in cancer prevention. The workshop built on joint activity in the area of micronutrient malnutrition, which was begun under the auspices of the Health Committee of the U.S.-Russia Commission on Economic and Technological Cooperation. Major support from the United States was provided by ODS, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and USAID. Participants included government and academic representatives from China, Finland, New Zealand, and the United States. The U.S. government representation included DHHS and USDA. The Russian representation included the Institute of Nutrition and the Research Center for Preventive and Therapeutic Nutrition, of the Russian Academy of Medical Sciences, and its Siberian division.

ODS cosponsored the International Workshop to Evaluate Research Needs on the Use and Safety of Medicinal Herbs, at the National Institute of Environmental Health Sciences (NIEHS), in Research Triangle Park, North Carolina, on September 22–23, 1998. The focus of the workshop was to identify and evaluate the major issues and key gaps in scientific research to ensure the safety of medicinal herbs. Topics included the benefits and risks associated with medicinal herbs and issues of methodology and product standardization. Representatives from ODS, the U.S. Food and Drug Administration, and other governmental, professional, and public interest groups participated in a panel discussion. Proceedings and a summary of the workshop are scheduled to be published in the NIEHS journal, *Environmental Health Perspectives,* in December 1998.

In addition, the ODS Director officially represented ODS and the NIH and chaired a symposium entitled Scientific Evaluation of Medicinal Herbs as Dietary Supplements and Remedies: Impact in Developed and Developing Countries, at the XVth Symposium on the Medicinal Plants of Brazil, in Aguas de Lindoia, Brazil, on October 14–17, 1998. At this meeting, the participants from Brazil, other Latin American countries, and the United States discussed the varied use of dietary supplements, research needs, and regulatory approaches in the respective countries.

Office of Rare Diseases

To stimulate research, the Office of Rare Diseases (ORD) solicits nominations from the NIH Institutes and Centers, for workshops or symposia on rare diseases or conditions, as requested by the U.S. Senate Committee on Appropriations. Primary consideration for support is given to a meeting if current research on a disease is lacking or lagging or if research is likely to be stimulated by the session. ORD provides support and cosponsors these conferences, workshops, or symposia.

In FY 98, 15 workshops on international activities were convened by NIAID; the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); NCI; the National Institute of Child Health and Human Development (NICHD); NIDDK; the National Heart, Lung, and Blood Institute (NHLBI); the National Human Genome Research Institute (NHGRI); the National Institute of Mental Health; and the National Institute of Neurological Disorders and Stroke (NINDS). ORD provided support and was included as a cosponsor of the scientific workshops.

NIAMS and ORD sponsored the International Centennial Meeting on Pseudoxanthoma Elasticum, which was held in Bethesda, Maryland, in November 1997. This conference was attended by scientists and physicians from Belgium, Canada, Israel, Italy, the Netherlands, South Africa, the United States, and Wales as well as several representatives of patient-advocacy organizations. Twenty-one internationally recognized scientists described the pathophysiology and genetics of pseudoxanthoma elasticum and reviewed in considerable detail the clinical manifestations of the disease. The proceedings of this meeting were published in the *Journal of Investigative Dermatology,* in May 1998.

A meeting on Emerging Opportunities in Scleroderma Research was cosponsored by NIAMS, with cooperation from NIAID, NHLBI, the NIH's ORWH and ORD, the Scleroderma Research Foundation, and the Scleroderma Federation. The meeting was held in Bethesda, Maryland, in December 1997, and was attended by participants from the United Kingdom and the United States. The goals were to facilitate interactions among scleroderma researchers and experts in relevant fields of study; to address the pathophysiology of scleroderma; to explore some of the new and emerging research findings in scleroderma; to identify research gaps and opportunities; and to foster research collaborations. Participants made presentations on mechanisms of microchimerisms and chronic graft-versus-host disease; endothelial cell pathology and vascular biology; genetics and other emerging areas of research on scleroderma; and opportunities in clinical trials. The meeting ended on an optimistic note that considerable progress had been made in understanding scleroderma, reasonable animal models had been described, and candidate genes had been identified. The chair of the meeting commented that both basic and clinical studies in scleroderma should be continued in parallel until they merge and lead to therapeutic interventions with opportunities for interaction in the future.

A workshop on pediatric scleroderma was held in Boston, Massachusetts, in July 1998. This meeting was held in conjunction with the 5th International Workshop on Scleroderma Research; attendees were from Australia, Brazil, Canada, Germany, the United Kingdom, and the United States. The participants included specialists in pediatric rheumatology, adult rheumatology, and dermatology. The workshop was convened by NIAID. Pediatric scleroderma is a rare, debilitating, and disfiguring disease that involves the skin, muscle, lungs, gastrointestinal tract, and kidneys. Topics covered in the workshop included the spectrum of scleroderma in children; localized scleroderma (pathogenesis, diagnosis, and management); gastrointestinal disease; lung disease; the status of clinical trials on assessment and management of scleroderma; the rationale for treatment with bone marrow ablation and reconstitution and the preliminary results of relevant studies; and survival of children with scleroderma. As a result of this workshop, a multicenter treatment protocol is being developed by the meeting participants. Because of the relative rarity of this disease, a multicenter trial to assess therapeutic outcome is warranted.

NIMH and ORD cosponsored a workshop on Heavy Metal Effects on Attention and Cognition in Children, in Moscow, Russia, in February 1998. Since the meeting, contact has been maintained with a number of workshop participants, and two have visited the NIH. One psychologist came to the NIMH Laboratory of Brain and Cognition to acquire additional experience with laboratory methods and techniques and has begun to translate the psychological tests used in this research into Russian. Since her return to Russia, she has been in contact with the Laboratory weekly; has begun to test schoolchildren in Moscow to improve her skills with these tests; and has started to train other Russian psychologists to use the tests. In addition, Russian researchers are planning to conduct assays of blood levels of lead in children, by using technology recently developed in conjunction with the Centers for Diseases Control and Prevention. Implementation of this plan depends on the availability of Russian funds.

The international Workshop to Elucidate the Neuropathology of Ataxia-Telangiectasia was held in Bethesda, Maryland, in March 1998. The workshop was sponsored by NINDS, ORD, and the Ataxia-Telangiectasia Children's Project. Participants and speakers were from Canada, France, Israel, Italy, Spain, the United Kingdom, and the United States. Neurological manifestations are the major source of disability in children and young adults with ataxia-telangiectasia (AT), a rare autosomal-recessive neurodegenerative disease. Since the gene for AT was discovered in 1995, much of the limited research has centered on the cancer and immune system problems associated with this disorder. Consequently, progress has been made in understanding and treating the nonneurological conditions associated with AT, but these advances have not been paralleled in the neurological aspects of the disease. Now, for the first time, the neurological degeneration can be more effectively addressed, because of the advent of several genetically engineered mouse models of AT that replicate aspects of the neuronal degeneration of the disease. This important development has broad implications, well beyond AT, because it addresses fundamental mechanisms (e.g., neuronal death) that are important in neurodegenerative disorders and ataxias of childhood and adulthood.

The workshop accomplished significant interchange and results. Participants identified the need for rigorous clinical evaluation of children with quantifiable ataxia, as shown by longitudinal assessment using motor examination and neuroimaging. In addition, investigators emphasized that various strains of mice should be used as animal models, to improve the comparability of neuropathology results among studies. As a result of new information presented at this meeting, two pilot clinical trials and new areas of brain pathology in animal models have been identified. New series of experimentation on AT and new findings on AT protein function also have ensued. In addition, several scientists who were not involved in AT research are now performing studies related to AT. NINDS program staff have been receiving more inquiries about research and grant applications, and NINDS has funded three investigators who presented pilot information at this meeting. The success and excitement of the conference have resulted in identification of new research investigators to participate in another AT meeting on neurodegeneration to be held in the near future. There also has been greater public and congressional attention to children with pediatric brain disorders. The president and cofounder of the Ataxia-Telangiectasia Children's Project testified before the U.S. House of Representatives' Commerce Committee's Subcommittee on Health and the Environment. He pointed out that research findings on AT may also be relevant to more common disorders such as Parkinson's disease.

Physicians and researchers have considered using gene therapy to treat patients with AT, but gene therapy (gene transfer) for any disease has proved to be extremely difficult in practice. Even though gene transfer has been tried in more than 1,000 patients with various diseases in the U.S. alone, no real success has yet been demonstrated. However, work is under way on a new technology to treat a genetic disease by repairing the mutation in the patient's genes.

Multiple system atrophy is a progressive neurodegenerative disease of undetermined cause that occurs sporadically, resulting in parkinsonism and cerebellar, autonomic, urinary, and pyramidal dysfunction, in many combinations. The disease affects both genders, usually beginning in middle age and progressing over intervals of 1–18 years. Median survival is about 9 years from the first symptom. Some efforts have been made to establish diagnostic criteria, but no consistent detailed guidelines have been developed. The Conference on Multiple System Atrophy was convened in Minneapolis, Minnesota, in April 1998. The meeting was cosponsored by NINDS; ORD; the American Autonomic Society; the American Academy of Neurology; Glaxo Wellcome, Inc.; Hoechst Marion Roussel; and Roberts Pharmaceutical Corporation. The conference's guidelines for diagnosis of multiple system atrophy have not yet been validated and will almost certainly require further modification in light of future experience. The meeting included participants from Austria, Canada, England, Germany, Italy, and the United States.

The 2nd International Scientific Symposium on Cyclic Vomiting Syndrome was held in Milwaukee, Wisconsin, in April 1998. This workshop was sponsored by NIDDK; ORD; the Dubin family and the Dhillon-Burkhardt family from Maryland; Janssen Pharmaceutica; Glaxo Wellcome, Inc.; Block and Company, Inc., Illinois; and Medtronic Synectics. Speakers and participants were from the United States and the United Kingdom. Cyclic vomiting syndrome is a rare unexplained disorder of children and some adults. It is characterized by recurrent prolonged episodes of severe vomiting, nausea, and prostration, with no apparent cause. The episodes are self-limited, usually ending suddenly, regardless of treatment, and tend to be similar in symptoms and duration. The child is healthy and free of symptoms between episodes. Five goals of clinical management of this syndrome were discussed at the symposium:

1. terminating an established episode;
2. abortion of an impending episode before vomiting begins;
3. making the patient with refractory symptoms comfortable until the episode subsides;
4. prophylaxis during episodes; and
5. recovery.

In May 1998, NIAID and ORD convened a workshop on the prospects for Gene Therapy of Inherited Phagocyte Disorders, in Seattle, Washington, in conjunction with the first meeting of the American Society of Gene Therapy. The inherited phagocyte disorders are a group of rare diseases that include chronic granulomatous disease, leukocyte adhesion deficiency, Chédiak-Higashi syndrome, and interferon γ receptor deficiency. These disorders are caused by genetic defects in phagocytes, which result in a decreased ability of these white blood cells to engulf and kill infectious agents. In Wiskott-Aldrich syndrome, both lymphocytes and phagocytes are affected by the genetic defect. The decreased ability to destroy infectious pathogens results in severe, recurrent, or life-threatening infections, or all three. The workshop brought together a group of distinguished scientists from the United States and Sweden to consider the available information and to make recommendations on the most important and promising research opportunities and approaches for development of effective gene therapy for this group of rare diseases. The participants agreed that several of the inherited phagocyte disorders are good candidates for gene therapy and that the problems in achieving highly efficient transduction of genes into hematopoietic stem cells are likely to be solved because of the large number of studies under way. Several research areas that would significantly contribute to the development of successful gene therapy for the inherited phagocyte disorders were identified. These areas include studies of phagocyte disorders treated with bone marrow transplantation; establishment of registries; enhancement and usefulness of genetically altered cells; and development of animal models.

The 1st International Meeting on Carney Complex and Related Disorders was held in Bethesda, Maryland, in May 1998. This meeting was sponsored by NICHD and ORD. Participants came from Canada, the United Kingdom, and the United States. Lentigines are common skin lesions similar to freckles. Some lentigines are part of genetic syndromes that are associated with inherited forms of neoplasias or other pathological processes of the cardiovascular, endocrine, and gastrointestinal systems. The familial lentiginoses include the LEOPARD and Peutz-Jeghers syndromes, Carney complex, and the newly described syndrome of dissected arterial tissue with lentiginosis. In the majority of the reported kindreds with lentiginosis and related syndromes, the lesions are inherited in an autosomal-dominant manner. The genetic loci and specific genes for these syndromes are under intense investigation. During the conference, discussions were held with participants from Canada and the United Kingdom, as well as from the NIH, to gain a better understanding of these disorders. Abstracts from this meeting were published in *Hormone and Metabolic Research,* in 1998.

NICHD, ORD, and the Nobel Forum of the Karolinska Institute, Stockholm, Sweden, sponsored the Mini-Symposium on Fetal Therapy, in Stockholm, in May 1998. The list of conditions that can be diagnosed prenatally for which therapeutic approaches are currently available or will soon be developed is expanding. Diagnosis of fetal disorders provides an opportunity for prenatal biomolecular, medical, pharmacological, or surgical intervention. The proceedings of this important meeting are expected to be published as a book.

NHGRI and ORD sponsored a technical meeting entitled Genomic Alterations in Genetic Disease: Mechanisms of Structural Rearrangement, which was held in Bethesda, Maryland, in June 1998, for researchers and physicians from Canada, the United Kingdom, and the United States. A technical summary was published in *Genome Research,* in 1998.

ORD joined NHGRI and NIMH to support a scientific forum on Carbohydrate-Deficient Glycoprotein Syndrome, which was held in Bethesda, Maryland, in June 1998. Physicians and scientists with expertise in the clinical medicine, glycobiology, and molecular biology of carbohydrate-deficient glycoprotein syndrome came from Canada, Belgium, Denmark, England, Germany, and the United States to attend the conference. They discussed their most recent findings and explored the clinical and scientific controversies in the field.

NIMH and ORD jointly sponsored an international research conference on Munchausen Syndrome by Proxy (Factitious Disorder by Proxy), which was held in conjunction with the 14th International Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions, in Stockholm, Sweden, in August 1998. Participants came from England, the Netherlands, Sweden, the United Kingdom, and the United States. The workshop focused on the current state of knowledge of the syndrome, including characteristics and course of episodes, characteristics and consequences for the perpetrators and victims, conceptual and methodological issues important in conducting studies, and research questions that must be addressed to improve the description and understanding of and intervention for this disorder. NIMH plans to publish a summary of the meeting.

A meeting on Joubert syndrome was cosponsored by NINDS and ORD. The conference was held in conjunction with the annual meeting of the Child Neurology Society, in Montreal, Quebec, in October 1998. Attendees came from Argentina, Brazil, Canada, Croatia, Finland, France, Israel, Japan, Switzerland, the United States, and the West Indies. Three journals have offered to devote an entire issue to hypoplasia of the vermis cerebelli in Joubert syndrome and related disorders. The *Journal of Child Neurology* plans to extend its coverage to the international community and would use this issue to disseminate information about the conference in Asia and Europe. There is still a need to clarify differential diagnosis of these syndromes for the research and clinical community. Although this disorder is perceived as rare, the number of diagnoses of Joubert syndrome reported by families highlights the importance of accurate diagnosis. Preparation of guidelines for diagnosis has been given a high priority by the Joubert Syndrome Foundation.

The 17th International Natural Killer Cell Workshop and the 5th Meeting of the Society for Natural Immunity were held at the Airlie Center, Warrenton, Virginia, in October 1998. The conferences were cosponsored by NCI and ORD, in conjunction with the Society for Natural Immunity. Nearly 200 scientists from Australia, Canada, Europe, Japan, and the United States attended the meetings.

NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

The National Center for Complementary and Alternative Medicine (NCCAM), formerly the Office of Alternative Medicine, continues to play a critical role internationally as a WHO Collaborating Center in Traditional Medicine. Additionally, NCCAM supports an electronic-mail listserve (TCAMNET), to link researchers in traditional complementary and alternative medicine worldwide. TCAMNET provides a forum for discussion of relevant topics in this field and facilitates the sharing of research-related information for investigators. More than 100 researchers in 30 countries subscribe to TCAMNET. Staff from NCCAM met with delegations from other regions and countries (West Africa, China, Germany, Japan, Mali, Sweden, and the United Kingdom) to discuss a variety of issues. NCCAM also cosponsored the 6th International Cochrane Colloquium on Systematic Reviews (of literature on clinical trials related to complementary and alternative medicine).

OFFICE OF EXTRAMURAL RESEARCH

In FY 98, the Deputy Director for Extramural Research again participated in several international activities. In February, she traveled to Thailand to chair the Social Services Research on Reproductive Health Committee of the WHO Human Reproductive Program. In that capacity, she met with the group working on training for the Human Reproductive Program. While in Thailand, the Deputy Director also met with scientists funded by the NIH and the Centers for Disease Control and Prevention and with Thai scientists, to discuss research on mother-to-infant transmission of HIV.

The Deputy Director has served since 1995 as the NIH representative on the board of trustees of the Human Frontiers in Science Program, a multinational program that supports international cooperation in molecular biology and research into brain functions, through the award of research grants and fellowships and through funding of related conferences and workshops. In 1998, the Deputy Director became cochair of the board of trustees, which met in Strasbourg, France, in March. The Deputy Director is also cochairing the planning for the third part of the celebration of the 10th anniversary of the Human Frontiers in Science Program, which is to take place in Washington, D.C., in 1999.

The Deputy Director participated in other activities for WHO. In May 1998, she traveled to Geneva, Switzerland, to participate in the WHO meeting on Global Burden of Disease, where she presented information on the NIH Computerized Retrieval of Scientific Information database system and discussed the importance of and mutual need for making research information available globally. In June, the Deputy Director served as a member of the U.S. delegation to the WHO World Health Assembly, in Geneva. In August, she chaired a meeting of the steering committee of WHO's Human Reproductive Program.

In September 1998, the Deputy Director traveled to Taipei, as a consultant to the Taiwan Department of Health. She was the featured speaker at a symposium, Maternal and Child Health Policy—A Vision Toward the 21st Century.

OFFICE FOR PROTECTION FROM RESEARCH RISKS

In FY 98, the Office for Protection From Research Risks (OPRR) successfully negotiated more than 350 assurances (Protection of Human Subjects Assurance Identification/Certification Declarations) to comply with DHHS regulations, for research conducted in 50 countries outside the United States. OPRR also negotiated 70 Animal Welfare Statements of Compliance with institutions in 27 countries outside the United States. In FY 98, OPRR's Human Subjects Assurance Branch established, and now maintains, regular contacts with the United Kingdom's Cancer Research Campaign, which includes 19 research sites, and with the European Organization for Research and Treatment of Cancer (EORTC), which includes 110 research sites. Both of these organizations collaborate with DHHS in international multicenter clinical trials.

The OPRR Deputy Director continues to serve as an advisor and liaison to the Standing Ethics Committee of the Canadian Medical Research Council. During 1998, council efforts were devoted to the preparation of the Tri-Council Policy Statement, entitled Ethical Conduct for Research Involving Humans, and the action plan for its implementation. In October 1998, the Deputy Director, OPRR, participated in the conference on Recent Clinical Developments in Asian Pacific Regions, in Taipei, Taiwan.

OPRR staff met with scientists from several countries in FY 98. Included were scientists and administrators from Australia, Belgium, Brazil, Canada, China, New Zealand, Taiwan, and member countries of EORTC. Staff also met with numerous U.S. Department of State science advisors posted in countries around the world.

OFFICE OF INTRAMURAL RESEARCH

The Senior Advisor to the Deputy Director for Intramural Research acts as the DHHS representative on the Interagency Arctic Research Policy Committee, which is chaired by the National Science Foundation. He also serves as the focal point for the human health aspects of the Arctic Monitoring and Assessment Program (AMAP). This program is one of the components of the Arctic Council, which in 1997 superseded the former Arctic Environmental Protection Strategy, to which the United States is one of eight arctic signatory nations. In 1998, the Senior Advisor was appointed as the DHHS liaison for Arctic Council activities.

In 1998, the Senior Advisor participated in several international meetings related to the AMAP effort. The AMAP-2 Human Health Subprogram group met in March in Aarhus, Denmark, and in October, in Reykjavik, Iceland, to discuss the next steps for the AMAP Human Health Program. In April, the AMAP Working Group met in Girdwood, Alaska. At the first Ministerial Meeting of the Arctic Council, in Iqualuit, Baffin Islands, Northwest Territories, in September, the United States accepted the chairmanship of the Arctic Council for 1998–2000. The Arctic Policy Group, convened by the Department of State to consider issues related to the Arctic Council, meets monthly.

On March 2–6, 1998, the Senior Advisor attended a Brookings Institution seminar on U.S.-European Union Relationships, in Maastricht, the Netherlands, and Brussels, Belgium. In March, he also presented a seminar at the Bone Research Laboratory, at Oxford University, England, about the Intramural Research Program of the NIH.

The Senior Advisor has met with dignitaries from various nations. He met with the new Norwegian Minister of Health to discuss possible agenda items for the new Director General of WHO, who is a former prime minister of Norway. He also met with the Director, Hong Kong Institute of Biotechnology, Ltd., and the Minister of Health, Taiwan.

III.

John E. Fogarty International Center for Advanced Study in the Health Sciences

INTRODUCTION

The John E. Fogarty International Center (FIC) for Advanced Study in the Health Sciences was established in 1968 by Executive Order and congressional action to promote research in the biomedical sciences through international cooperation and to serve as the organizational locus for National Institutes of Health (NIH) international activities. In 1998, FIC celebrated its 30th year as the NIH component dedicated to promoting research and training in global health.

Since its inception, the Center has been instrumental in forging partnerships between U.S. and foreign scientists and research institutions, initially by means of FIC-supported individual fellowships and exchange programs and bilateral agreements. For example, more than 900 U.S. scientists have undertaken research at foreign centers of excellence in Europe and elsewhere under the FIC Senior International Fellowship Program, and over 3,000 postdoctoral scientists from more than 60 nations have participated in research at U.S. universities and the NIH as International Research Fellows. The FIC intramural Scholars-in-Residence Program has brought more than 200 scientific leaders from across the world to the NIH campus to pursue advanced studies on the frontiers of biology and medicine. Thousands more have worked in NIH laboratories through the visiting programs administered by FIC. Collectively, these investigators now represent a prominent component of the international biomedical research enterprise.

Today, in a world that is increasingly challenged to respond to a growing number of global health threats, FIC is dedicated to mobilizing scientific resources to reduce ever-growing disparities in global health. FIC-supported research training and small grants programs, many in partnership with several NIH Institutes and other Federal agencies, all aim to expand cooperation between U.S. scientists and their partners overseas. Research grants foster international collaborations between NIH-supported U.S. scientists and scientists in developing countries and newly emerging democracies, while training grants aim to build research capacity in parts of the world that are most affected by global problems, such as emerging infectious diseases, population growth, and the health risks of environmental degradation.

A nation's health has profound repercussions on social and economic well-being. A key role of today's FIC is to bring together diverse scientific disciplines to confront major health concerns that affect populations in the United States and around the world. To achieve this goal, FIC continues to establish new partnerships among institutions involved in global health, to ensure that research efforts translate into public health tools and interventions for the benefit of all people.

AIDS INTERNATIONAL TRAINING AND RESEARCH PROGRAM

Through the AIDS International Training and Research Program (AITRP), FIC sponsors U.S. schools of medicine and public health to provide training for foreign scientists from developing countries through a variety of training options. The training is designed (a) to increase the capacity of scientists to pursue biomedical and behavioral research on acquired immunodeficiency syndrome (AIDS); (b) to use acquired skills in clinical trials and prevention and related research; and (c) to stimulate cooperation and sharing of research knowledge.

As a result of a review of AITRP undertaken in fiscal year 1997 (FY 97), the mission of the Program was refined to focus on multidisciplinary biomedical and behavioral approaches to prevent infection with human immunodeficiency virus (HIV). On the basis of this new program emphasis, FIC issued a new Request for Applications in FY 98 that resulted in six new grants and eight competing renewals (Table III-1). These awards were made possible by collaborative funding from the National Institute on Drug Abuse (NIDA), the National Institute of Dental Research (NIDR), the National Institute of Mental Health (NIMH), and the NIH Office of AIDS Research.

Since the inception of AITRP, more than 1,500 scientists from nearly 100 countries and territories have received training in the United States. In addition, more than 600 courses have been conducted in 60 countries. These courses provided short-term training for more than 42,000 students and health professionals. AITRP now constitutes the single largest global training program for HIV and AIDS research. One indicator of progress is the success of the Program in generating scientific findings and resulting publications. In FY 98, FIC trainees authored or coauthored more than 100 research reports that were published in prominent scientific journals. Key areas of emphasis are presented here.

Vitamin A, Other Micronutrients, and HIV Infection in Children

Through ongoing studies by scientists at Johns Hopkins University, Baltimore, Maryland, and Harvard University, Cambridge, Massachusetts, AITRP continued to sponsor research on nutritional supplementation, including vitamin A and other micronutrients, as an approach to decreasing mother-to-child transmission of HIV. FIC and the National Institute of Child Health and Human Development (NICHD) are continuing to sponsor ongoing studies of HIV-infected mothers in Malawi and Tanzania. Another joint FIC/NICHD study in Uganda is testing whether nutritional supplementation to children born to HIV-infected mothers forestalls clinical problems in infants who are seropositive for HIV.

Research has also been conducted on the potential role of micronutrient supplementation as a prophylactic and therapeutic measure for persons infected with HIV. Together with scientists at Muhimbili University College of the Health Sciences, Dar es Salaam, Tanzania, scientists at Harvard University conducted an interventional trial to measure the effects of multivitamin supplements on birth outcomes in HIV-infected women. They found that daily doses of multivitamins decreased the risk of fetal death, low birth weight, and preterm birth and resulted in a significant increase in the number of T cells in HIV-infected mothers. (T cells are essential for the control of virus levels in infected persons).

HIV Transmission and Disease Progression

In conjunction with the National Institute of Allergy and Infectious Diseases (NIAID), FIC is supporting studies in Malawi to determine whether vitamin A supplementation combined with standard therapies for tuberculosis is more effective in improving health outcomes than standard tuberculosis therapy alone.

In a collaborative study cosponsored by FIC, researchers at the Ministry of Health and Makerere University, Kampala, Uganda, and the Centers for Disease Control and Prevention (CDC) are working with scientists at Case Western Reserve University, Cleveland, Ohio. These investigators have made significant progress toward developing practical and affordable prevention measures to reduce the burden of tuberculosis in HIV-infected adults who were positive for purified protein derivative (PPD). The study indicates that a 3- to 6-month course of prophylactic treatment for tuberculosis in a study population of HIV-infected adults significantly reduced the risk of active infection and transmission.

A community-based study in Uganda that was carried out by AITRP trainees from Uganda, through Case Western Reserve University, Columbia University, New York, New York, and Johns Hopkins University, Baltimore, showed that community-wide prophylactic therapy for sexually transmitted diseases does not reduce heterosexual transmission of HIV. The purpose of the study was to determine whether aggressive prevention of sexually transmitted diseases would reduce the burden of HIV in a well-defined population.

TABLE III-1.

AIDS International Training and Research Program, Fiscal Year 1998

Principal Investigators/Institutions	Major Collaborating Countries
Epidemiology Programs	
[a]Dr. Adaora A. Adimora University of North Carolina, Chapel Hill Chapel Hill, N.C.	Cameroon, China
[b]Dr. Marianna K. Baum University of Miami Miami, Fla.	Brazil, Colombia, Dominican Republic, Honduras, Zambia
[b]Dr. Chris Beyrer Johns Hopkins University Baltimore, Md.	Brazil, Dominican Republic, Ethiopia, Haiti, India, Malawi, Malaysia, South Africa, Thailand, Uganda
[a]Dr. William A. Blattner University of Maryland Baltimore, Md.	Barbados, Brazil, Jamaica, Trinidad and Tobago
Dr. Jack A. DeHovitz State University of New York Brooklyn, N.Y.	Armenia, Czech Republic, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland
[a]Dr. Carlos del Rio Emory University Atlanta, Ga.	Georgia, Mexico, Vietnam
[b]Dr. Roger Detels University of California, Los Angeles Los Angeles, Calif.	Cambodia, China, India, Mexico, Myanmar, Vietnam
[b]Dr. Max Essex Harvard University Boston, Mass.	Botswana, Senegal, Tanzania, Thailand
[a]Dr. Lee H. Harrison University of Pittsburgh Pittsburgh, Pa.	Brazil
[b]Dr. Warren D. Johnson, Jr. Cornell University Medical College New York, N.Y.	Brazil, Haiti
Dr. Salim Abdool Karim Columbia University New York, N.Y.	Botswana, Namibia, South Africa
[b]Dr. Joan Kreiss University of Washington Seattle, Wash.	Kenya, Mozambique, Peru, Thailand
Dr. Kenneth Mayer Brown University Providence, R.I.	Indonesia, Philippines
[a]Dr. Michael H. Merson Yale University New Haven, Conn.	Newly Independent States of the Former Soviet Union, Russia
[b]Dr. Arthur L. Reingold University of California, Berkeley Berkeley, Calif.	Botswana, Brazil, Côte d'Ivoire, Thailand, Vietnam, Zimbabwe
[a]Dr. Sten H. Vermund University of Alabama Birmingham, Ala.	Bangladesh, Mongolia, Pakistan, Zambia
[b]Dr. Christopher Whalen Case Western Reserve University Cleveland, Ohio	Uganda
Postdoctoral Programs	
Dr. Chris Beyrer Johns Hopkins University Baltimore, Md.	Brazil, Dominican Republic, Ethiopia, Haiti, India, Malawi, Malaysia, South Africa, Thailand, Uganda
Dr. John Fahey University of California, Los Angeles Los Angeles, Calif.	Brazil, China, India, Mexico, Thailand, Vietnam
Dr. Joan Kreiss University of Washington Seattle, Wash.	Kenya, Mozambique, Peru, Thailand
Dr. Gwendolyn Scott University of Miami Miami, Fla.	Brazil, Haiti, Romania, Zambia

[a]New grants in fiscal year 1998.

[b]Competing renewals in fiscal year 1998.

Vaccine Development

FIC trainees continued to monitor HIV variants and provide epidemiologic data required for the development of candidate vaccines and the design and evaluation of trials of vaccine efficacy. AITRP has established a core of highly trained clinical and epidemiologic investigators in regions of the world that may become sites for international testing of HIV vaccine candidates. These scientists also are positioned to support research on other HIV interventions, such as antiviral treatments, antibiotics, microbicides, and programs to modify high-risk behaviors. This support has been put in place through close collaboration with the NIAID HIV Network Program, which has established a baseline of epidemiologic data and cohorts of volunteers for future efficacy trials of vaccine and other agents.

TUBERCULOSIS INTERNATIONAL TRAINING AND RESEARCH PROGRAM

In FY 98, FIC provided funding for competing supplemental awards under the Tuberculosis International Training and Research Program, a collaborative Program with NIAID, CDC, and the U.S. Agency for International Development. In the first review cycle, seven awards were made to U.S. universities and institutions as supplements to existing grants under AITRP or the International Training and Research Program in Emerging Infectious Diseases (Table III-2), to extend existing research investments in these areas. The supplements aim to build health research efforts and public health capacity globally to better respond to the threat posed by tuberculosis in general and multidrug-resistant tuberculosis in particular. Long-term objectives include the following:

- strengthening laboratory infrastructure in support of future tuberculosis surveillance and research;
- building public health capacity for surveillance and clinical trials of promising new interventions and therapies for tuberculosis; and
- enhancing the capability of developing countries to manage programs and conduct operational research related to prevention and control of the disease.

These awards are designed (a) to prepare current and future generations of researchers and public health workers around the world to confront the global tuberculosis epidemic and (b) to establish and maintain centers for clinical research in and treatment and prevention of tuberculosis, all of which will play a major role in the fight against the reemergence and continuing spread of this disease.

TABLE III- 2.

Tuberculosis International Training and Research Program, Fiscal Year 1998

Program Directors	Major Collaborating Countries
Dr. Marianna K. Baum University of Miami School of Medicine Miami, Fla.	Dominican Republic, Honduras
Dr. Christopher Beyrer Johns Hopkins University Baltimore, Md.	Brazil, Haiti, India, Peru, South Africa
Dr. Warren D. Johnson, Jr. Cornell University Medical College New York, N.Y.	Brazil, Haiti, Peru
Dr. Salim Abdool Karim Columbia University New York, N.Y.	South Africa
Dr. Dale Morse David Axelrod Institute New York State Department of Health Albany, N.Y.	Czech Republic, Georgia, Hungary, Poland, Russia
Dr. Lee Riley University of California School of Public Health Berkeley, Calif.	El Salvador, Guatemala, Mexico
Dr. Christopher Whalen Case Western Reserve University Cleveland, Ohio	Mexico, Uganda

INTERNATIONAL COOPERATIVE BIODIVERSITY GROUPS

The contraction of natural habitats and, in particular, the destruction of species-rich tropical rainforests will have profound economic, social, and scientific consequences. In partnership with NIH research Institutes and other Federal agencies, FIC leads an interagency effort to promote economic development and ecological conservation through drug-discovery research on natural products. This initiative supports the development of interdisciplinary research in which U.S. institutions and those in developing countries collaborate in the study of important biological resources indigenous to the developing countries.

International Cooperative Biodiversity Groups (ICBGs) were established in FY 94 to discover new therapeutic agents for a broad range of human diseases and agricultural applications. Therapeutic and preventive areas receiving attention include cancer, AIDS, Alzheimer's disease, drug addiction, contraception, cardiovascular disorders, bacterial and viral diseases, tuberculosis, malaria, and leishmaniasis. Agents are derived from natural products from numerous species of plants, fungi, and insects. Integrated into the research efforts are strategies to preserve biological diversity by developing knowledge for resource management and opportunities for local economic benefits from commercial development of discoveries. The projects supported by this program include screening and description of biologically active organisms; study of the chemistry of natural products; research on traditional medicines and practices related to their use in indigenous cultures; comparison of modes of drug-discovery research; and training and career development for scientists from cooperating nations.

The three principal sponsors of the ICBG program—the NIH, the National Science Foundation, and the Foreign Agricultural Service of the U.S. Department of Agriculture—jointly announced six new awards under this program in FY 98. Participating

TABLE III-3.

International Cooperative Biodiversity Groups, Fiscal Year 1998

Principal Investigator/ U.S. Institutions	Source Countries	Foreign Collaborating Investigators/Institutions	Domestic Collaborating Investigators/Institutions
Dr. Brent Berlin University of Georgia Athens, Ga.	Mexico	Dr. Luis Garcia El Colegio de la Frontera Sur San Cristobal de Los Casas, Chiapas Dr. Robert Nash Molecular Nature Ltd. Wales, U.K.	Dr. Elois Ann Berlin University of Georgia Dr. David Duett University of Georgia
Dr. Phyllis Coley Smithsonian Tropical Research Institute Panama City, Panama	Panama	Dr. Mababir Gupta University of Panama Panama City Dr. Eduardo Ortega Gorgas Memorial Hospital Panama City	Dr. Todd Capson STRI Dr. Leslie Harrison Monsanto Co. Dr. Tom Kursor University of Utah Dr. Don Windsor STRI
Dr. David Kingston Virginia Polytechnic and State University Blacksburg, Va.	Madagascar	Dr. Rabodo Andriantsiferana Center for Natural Products Research Antananarivo	Dr. James Miller Missouri Botanical Garden Dr. Russell Mittermeier Conservation International Dr. J. J. Kim Wright Bristol-Myers Squibb Pharmaceutical Research Institute
	Suriname	Mr. Stan Malone Conservation International Suriname Paramaribo Dr. Marga Verkhoven University of Suriname Herbarium Paramaribo Dr. Jan Wisse Bedrijf Geneesmidden Voorzenig Suriname Paramaribo	
[a]Dr. Walter Lewis Washington University St. Louis, Mo.	Peru	Dr. Gerardo Lamas San Marcos National University of Peru Lima Mr. Cesar Sarasara Confederation of Amazonian Nationalities of Peru Lima Dr. Abraham Vaisberg Peruvian Cayetano Heredia University Lima	Dr. Margaret Wideman Monsanto-Searle Pharmaceutical Research
Dr. Brian Schuster Walter Reed Army Institute of Research Washington, D.C.	United States	Dr. Maurice Iwu Bioresources Development and Conservation Washington, D.C.	Dr. Francisco Dallmeier Smithsonian Institution Dr. Joan Jackson Walter Reed Army Institute of Research Dr. Elizabeth Losos Smithsonian Institution Dr. Wilbur Milhous Walter Reed Army Institute of Research
	Cameroon	Dr. Johnson Ayafor University of Dschang Dschang	
	Nigeria	Dr. Iwe Paul Akubue University of Nigeria Nsukka	
Dr. Dal Soejarto University of Illinois Chicago, Ill.	Laos	Dr. Boun Hoong Southavong Research Institute for Medicinal Plants Vientiane	Dr. Melanie O'Neill Glaxo Wellcome United Kingdom Dr. John Pezzuto University of Illinois
	Vietnam	Dr. Li Thi Xuan National Center for Natural Sciences and Technology Hanoi	

TABLE III-3. *(Continued)*

International Cooperative Biodiversity Groups, Fiscal Year 1998

Principal Investigator/ U.S. Institutions	Source Countries	Foreign Collaborating Investigators/Institutions	Domestic Collaborating Investigators/Institutions
Dr. Barbara Timmermann University of Arizona Tucson, Ariz.	Argentina	Dr. Rodolfo Casamiquela CONICET Patagonia Dr. Enrique Suarez National Institute of Agricultural Technology Buenos Aires	Dr. Scott Franzblau Louisiana State University Dr. Deborah Galinis American Cyanamid Co. Dr. William Maiese Wyeth-Ayerst Pharmaceuticals
	Chile	Ms. Gloria Montenegro Catholic University of Chile Santiago Dr. Edgardo Saavedra Patagonia University	
	Mexico	Dr. Robert Bye National Autonomous University of Mexico Dr. Rachel Mata National Autonomous University of Mexico	

[a] Continuing through calendar year 1999.

NIH Institutes, in addition to FIC, are the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), NIAID, NIDA, and NIMH. Each of the seven active ICBGs, including one continuing award, comprises diverse private and public institutions, including universities, pharmaceutical companies, and environmental organizations in 11 countries (Table III-3).

For each ICBG, preserved specimens are obtained and stored in at least one institution in the source country and one in the United States. Information on these specimens is recorded in geographic information systems and other computer databases in each country.

ICBG trainees include technicians, faculty, and graduate, postgraduate, and postdoctoral students. Training includes long-term study and work in degree programs, as well as short technical courses and workshops in biodiversity description and management and biomedical science. More than 400 students and technicians from institutions in at least 10 developing countries have received or are receiving training through ICBGs. This training involves numerous exchanges between universities and pharmaceutical companies in the United States and universities in the host countries.

Other efforts to build research capacity include equipment transfers to collaborators in the developing countries, both through government funding and directly from commercial partners. Commonly transferred laboratory equipment includes that related to the preparation, extraction, storage, and microbiological screening of specimens and the isolation and identification of chemical constituents. Equipment purchases include herbarium storage cases, computers, software, and field equipment to aid with description and management of biodiversity. Efforts to develop local infrastructure include the purchase of vehicles, renovation of laboratories and herbaria, and support of a medical clinic.

FOGARTY INTERNATIONAL RESEARCH COLLABORATION AWARD

To foster research partnerships between U.S. scientists and their colleagues in regions of the world that provide new scientific opportunities, FIC established the Fogarty International Research Collaboration Award (FIRCA) in FY 92. These small research grants were designed to support collaborative ties with Latin America and the Caribbean and Central and Eastern Europe, including the Newly Independent States of the Former Soviet Union. In FY 94, regional eligibility was expanded to include the countries of Africa; Asia (except Hong Kong, Japan, Singapore, South Korea, and Taiwan); the Middle East; and the Pacific Ocean islands (except Australia and New Zealand). In FY 98, there were 104 active projects: 63 noncompetitive continuing awards and 41 new awards, including 6 competitive continuing awards (Table III-4).

Through the FIRCA program, funds are provided to U.S. researchers to purchase supplies, materials, and small equipment for the foreign collaborator's laboratory and to provide travel support for cooperative international studies (up to 25% of the grant award). These grants of $20,000 per year ($32,000 beginning in FY 99) for up to 3 years are awarded competitively as adjuncts to NIH-supported research projects. Beginning in FY 99, a stipend of $5,000 will be allowed for the foreign collaborator. U.S. participants must be the principal investigators of an ongoing NIH research project grant during at least the 1st year of the award period.

FIRCA supports a broad range of international cooperative research in areas such as the biology of the brain, cell-mediated immune responses, emerging and reemerging infectious diseases, pharmacological therapeutics, genetics, and women's health issues. Examples of FIRCA projects undertaken in FY 98 are presented here.

Scientists from the University of Iowa, Iowa City, are collaborating with Argentinean scientists at the Instituto de Investigación Medica, Córdoba, to investigate regulation of thirst and salt appetite by the kidney and nervous system. The goal of the

TABLE III-4.

Fogarty International Research Collaboration Awards by Region and Country, Fiscal Year 1998

Region/Country	No.
Europe, Russia, and NIS[a]	
Russia	24
Hungary	7
Czech Republic	6
Poland	3
Estonia	3
Croatia	3
Bulgaria	2
Slovakia	2
Ukraine	2
Belarus	1
Germany	1
Slovenia	1
Latin America and the Caribbean	
Argentina	8
Mexico	5
Chile	3
Colombia	1
Ecuador	1
Peru	1
Uruguay	1
Africa	
South Africa	2
Cameroon	1
Kenya	1
Trinidad and Tobago	1
Uganda	1
Zimbabwe	1
Asia, India, and Middle East	
China	6
Israel	6
India	5
Turkey	2
Bangladesh	1
Fiji Islands	1
TOTAL	**104**

[a] NIS = Newly Independent States of the Former Soviet Union.

study is to examine the role of the brain's amygdala in control of the appetite for sodium and the balance of bodily fluids. New information will advance knowledge of how the brain processes information related to bodily fluids and cardiovascular homeostasis.

Researchers from the University of Alabama, Birmingham, in collaboration with scientists at the Centro de Virologia Animal, Buenos Aires, Argentina, are attempting to characterize the incorporation of envelope glycoprotein of the simian immunodeficiency virus (SIV) into budding particles, the step in SIV morphogenesis that confers infectivity to virions. These studies will permit a better understanding of a key step in the SIV life cycle and may be useful for rational design of strategies to block the infectivity of the closely related human immunodeficiency virus type 1 and type 2 (HIV-1 and HIV-2).

Investigators from Georgetown University, Washington, D.C., are collaborating with scientists at the University of Yaoundé, Cameroon, to study immune system dysfunction in malaria and concomitant measles. Mortality in measles outbreaks in malaria-plagued areas of Cameroon often has been associated with secondary bacterial infections. Lower levels of measles antibodies have been observed in persons with malaria parasitemia than in those who were parasite negative. These findings have important public health implications for the endemic area, because measles vaccination is probably less effective if given during the season of high malaria incidence than at other times of the year. Persons who are vaccinated for measles at Yaoundé hospital will be invited to return and have their blood drawn at regular intervals, and efforts will be made to determine the levels and durations of measles antibodies and malarial antibodies, as well as other indicators of immune system responses. It is hoped that this work will provide enough data to form the basis for the most effective and efficient vaccination regimens.

Researchers at the University of California, Santa Cruz, are collaborating with scientists at the University of the South Pacific, Suva, Fiji, to study possible antitumor compounds from the biologically important marine sponge *Jaspis coriacea,* which contains compounds that have been shown to kill breast tumor cells in vitro. *J. coriacea* is common throughout the Indo-Pacific region and is especially abundant in reefs throughout the Fiji Islands. Previous work has established that distribution of the types of compounds found in *J. coriacea* samples appear to vary with the season and with geographic location, but the factors that cause variability are not understood. This FIRCA study will examine *J. coriacea* in greater detail, including the chemical variation of its antitumor compounds as a function of ecological factors.

TABLE III-5.

AIDS-Fogarty International Research Collaboration Awards by Region and Country, Fiscal Year 1998

Region/Country or Area	No.
Europe, Russia, and NIS[a]	
United Kingdom	7
Czech Republic	3
Germany	2
Sweden	2
France	1
Italy	1
Poland	1
Russia	1
Latin America and the Caribbean	
Argentina	2
Peru	2
Africa	
Botswana	1
The Gambia	1
Kenya	1
Namibia	1
South Africa	1
Asia, India, and Middle East	
Taiwan	3
India	2
Vietnam	1
North America	
Canada	1
TOTAL	**34**

[a] NIS = Newly Independent States of the Former Soviet Union.

Scientists from the University of North Carolina, Chapel Hill, and Moscow State University, Russia, continued a collaboration begun in FY 94 and renewed in FY 98. Groundbreaking experiments are leading to a better understanding of the mechanisms responsible for most types of cell differentiation into various tissue types in multicellular organisms. The current hypothesis is that similar basic mechanisms lead to development of very different tissue systems in two cell types, because of their different microtubular systems.

In addition to FIRCA, small collaborative grants are available to U.S. principal investigators who have NIH grants for international collaborative projects related to HIV/AIDS. The HIV/AIDS and Related Illnesses FIRCA (AIDS-FIRCA) provides up to $20,000 per year ($32,000 beginning in FY 99) for a maximum of 3 years. Regional eligibility is not limited. In FY 98, FIC made 34 AIDS-FIRCAs (Table III-5). Examples of accomplishments under the AIDS-FIRCA program are presented here.

Scientists from Colorado State University and the University of St. Andrews, Scotland, are working to identify unique *Mycobacterium tuberculosis* enzymes as possible targets in an effort to develop drugs that will inhibit the growth of *M. tuberculosis*.

INTERNATIONAL TRAINING AND RESEARCH PROGRAM IN ENVIRONMENTAL AND OCCUPATIONAL HEALTH

In FY 95, FIC cooperated with the NIH's National Institute of Environmental Health Sciences (NIEHS) and CDC's National Institute for Occupational Safety and Health (NIOSH) to develop an International Training and Research Program in Environmental and Occupational Health. This Program supports training and research in general environmental health and occupational health for scientists from developing countries and emerging democracies.

The Program helps to increase national capacity to identify and address health risks related to environmental change and degradation. It fosters cooperative research with regions of the world having relatively high contamination levels that present opportunities (a) to study the effects of environmental agents and occupational dangers on human health and (b) to develop new interventions.

In FY 95, seven awards were made to U.S. universities, including schools of medicine and public health. Areas of research and training that are addressed include studies of the biological effects of environmental contaminants; epidemiology of environmental- and work-related diseases; and investigation of the relationships between environmental changes and the rise of infectious diseases. Trainees include health scientists, clinicians, epidemiologists, toxicologists, engineers, industrial hygienists, chemists, and allied health workers.

In FY 96, an additional five awards were made with increased support from NIEHS and NIOSH and from a new partner—the National Center for Environmental Health, CDC. Projects funded in FY 96 include training and research in occupational medicine; epidemiology and health; environmental toxicology and assessment of exposure to environmental agents; industrial hygiene; air and water pollution; and biomedical engineering.

One additional award was made in September 1997 for studies related to environmental epidemiology, air and water pollution, and risk assessment. The number of collaborating countries in this Program is now 28. Some research and program accomplishments in FY 98 (Table III-6) are presented here.

Investigators from the University of California, Los Angeles, the Mexican Federal District Department, Mexico City, and the National Council for Science and Technology of Mexico are evaluating health problems related to the quality of drinking water in the Mexico City metropolitan area. This research and training project is part of an ongoing study of the region's water quality from a microbiological perspective. It is fo-

TABLE III-6.

Environmental and Occupational Health International Training and Research Programs, Fiscal Year 1998

Principal Investigators	U.S. Institutions	Collaborating Countries
Dr. Scott Barnhart	University of Washington Seattle, Wash.	Costa Rica Ecuador Mexico Nicaragua Thailand Vietnam
Dr. David Carpenter	State University of New York at Albany Rensselaer, N.Y.	Czech Republic Hungary Poland Romania Ukraine
Dr. Thomas Cook	University of Iowa Iowa City, Iowa	Czech Republic Hungary Romania Slovakia Slovenia
Dr. George Delclos Dr. Sarah Felknor	University of Texas Houston, Tex.	Colombia Costa Rica Mexico Venezuela
Dr. Douglas Dockery	Harvard School of Public Health Boston, Mass.	China
Dr. John Froines	University of California Los Angeles, Calif.	Mexico
Dr. Ian Greaves	University of Minnesota Minneapolis, Minn.	Philippines
Dr. Ellen Silbergeld	University of Maryland Baltimore, Md.	
Dr. Daniel Hryhorczuk	University of Illinois Chicago, Ill.	Belarus Lithuania Ukraine
Dr. Dana Loomis	University of North Carolina Chapel Hill, N.C.	Brazil
Dr. Steven Markowitz	Queens College Flushing, N.Y.	Brazil Chile Mexico
Dr. Rolando Merino	Mt. Sinai School of Medicine New York, N.Y.	
Dr. Evangelos Petropoulos	Michigan State University East Lansing, Mich.	Bulgaria Romania
Dr. Thomas Robins	University of Michigan School of Public Health Ann Arbor, Mich.	Botswana Lesotho South Africa Zimbabwe
Dr. Kirk Smith	University of California Berkeley, Calif.	China India South Africa

TABLE III-7.

International Training and Research Program in Population and Health, Fiscal Year 1998

Principal Investigators	U.S. Institutions	Collaborating Countries
Dr. Linda Adair	University of North Carolina Chapel Hill, N.C.	China Philippines Thailand
Dr. P. Michael Conn	Oregon Health Sciences University Beaverton, Ore.	Chile Mexico
Dr. Frank French	University of North Carolina Chapel Hill, N.C.	Brazil Chile China India Kenya
Dr. John Herr	University of Virginia Charlottesville, Va.	China India
Dr. David Lam	University of Michigan Ann Arbor, Mich.	China Nepal Thailand Vietnam
Dr. Jerome Strauss	University of Pennsylvania Philadelphia, Pa.	Argentina Chile Mexico Uruguay
Dr. Tukufu Zuberi	University of Pennsylvania Philadelphia, Pa.	Bangladesh Ethiopia Ghana Kenya Lesotho Malawi Mexico South Africa Uganda Zimbabwe

cusing on organic chemical analyses of bacterial pathogens by traditional and new molecular methods, with the goal of reducing or eliminating factors that contribute to health problems.

Scientists from the University of Minnesota, Minneapolis, and the University of Maryland, College Park, in collaboration with Philippine scientists from the University of the Philippines and the Philippine Malaria Research Institute, Manila, are developing research protocols to examine the extent of environmental mercury contamination associated with gold mining and ore processing on the island of Mindanao. Discussions with local officials, managers, and technical staff at ore-processing facilities and with affected community groups have indicated extensive mercury pollution. Because the area also has high endemic rates for malaria and tuberculosis, the protocols will measure urinary mercury levels present in miners, ore processors, and local community members, as well as the prevalence of malaria and tuberculosis among these groups. The purpose of the study is to investigate possible interactions among mercury contamination, T-cell dysfunction, and infectious disease rates.

Researchers at the University of Illinois, Chicago, and investigators at the Ministries of Health and Environmental Protection, Kyiv, Ukraine, and several institutions within the Ukrainian Academy of Medical Sciences, designed and implemented an environmental epidemiologic study of the health of 3-year-old children in Mariupol. This work included environmental characterization, a health assessment study, and components of risk assessment. Data also were collected for an assessment of exposure to organochlorine pesticides and to polychlorinated biphenyls (PCBs), polyaromatic hydrocarbons (PAHs), and mercury, as well as the relationships between exposure to heavy metals and childhood development and between PAH exposure and immune function.

Investigators from the University of Washington, Seattle, in collaboration with Vietnamese researchers at the National Institute of Occupational and Environmental Health, Hanoi, designed a questionnaire and completed collection of data on workers' risk of exposure to silica in Vietnamese industries. The questionnaire was administered across 61 provinces, and the data obtained included information on the numbers of workers exposed to silica and on all identified cases of exposure. This risk profile was specifically applied in Binh Dinh Province to investigate acute silicosis that was thought to be related to exposure to a high content of quartz, particularly in the mining industry. A preliminary risk assessment was completed, and a more in-depth study of silica exposure was developed to further investigate the epidemiology of exposure.

INTERNATIONAL TRAINING AND RESEARCH PROGRAM IN POPULATION AND HEALTH

In FY 95, in cooperation with NICHD, FIC developed the International Training and Research Program in Population and Health, to support training and research programs in population-related sciences for scientists and health professionals from developing countries. The Program enhances domestic population research programs by enabling NIH grant recipients to extend the geographic base of their work internationally. The National Institute on Aging joined the program in January 1999.

In FY 95, grants were awarded to seven U.S. universities, including schools of medicine and public health, to collaborate with institutions abroad in training and research activities in population-related sciences (Table III-7). These grants, including research partnerships in 20 countries, continued in FY 98. Funded projects cover training and research in basic reproductive biology and immunology; development of contraceptives; evaluation of contraceptives in relation to reproduction; the epidemiology of reproduction; and social, demographic, and behavioral factors that influence population dynamics.

In collaboration with scientists at the University of North Carolina, Chapel Hill, a Chinese scientist is studying human epididymal genes that code for sperm maturation proteins. This Chinese predoctoral scientist, whose training program at the University of North Carolina is part of a degree program at the Shanghai Institute of Biochemistry, has cloned and sequenced a gene coding for a 30-kilodalton protein that is expressed in both humans and rats. In addition, he is searching for novel nuclear (orphan) receptors in the human epididymis that may contribute to the regulation of epididymal function and thereby influence the acquisition of fertilizing ability of sperm.

Investigators at the University of Virginia, Charlottesville, are collaborating with investigators at the Indian Institute of Science, Bangalore, in research on immunodominant sperm antigens recognized by antisperm antibodies in the sera of infertile men and women that contain antisperm antibodies. In this study, sera from 15 infertile men were analyzed by Western blot of two-dimensional gels containing human sperm proteins. These isoantigens and autoantigens on the sperm surface, which are recognized by antibodies in the sera of infertile patients, are being microsequenced, in efforts to clone the corresponding complementary DNAs (cDNAs) and test their efficacy as contraceptives.

INTERNATIONAL TRAINING AND RESEARCH PROGRAM IN EMERGING INFECTIOUS DISEASES

In FY 97, in collaboration with NIAID, FIC funded 13 awards to U.S. universities to expand NIH research training efforts in studies of emerging infectious diseases. NIDR also contributed resources to this Program—the International Training and Research Program in Emerging Infectious Diseases (ITREID). The long-term objective is to train teams of scientists in regions of the world that provide unique opportunities to understand the fundamental biology, epidemiology, and control of emerging microbial diseases. The Program focuses on research training in the changing patterns of infectious diseases, including genetic evolution, geographic spread, and social factors such as economic development and land use. Funded projects include programs that address emerging and reemerging viruses; parasitic infections; bacterial and rickettsial diseases; and related issues such as microbial resistance to drugs. This Program aims to strengthen the capacity of scientists to understand and respond to disease outbreaks more effectively in the 22 collaborating countries and globally (Table III-8). Some of the research highlights in the ITREID Program for FY 98 are presented here.

TABLE III-8.

International Training and Research Program in Emerging Infectious Diseases, Fiscal Year 1998

Principal Investigators	U.S. Institutions	Collaborating Countries
Dr. Robert Gilman	Johns Hopkins University Baltimore, Md.	Peru
Dr. Richard Guerrant	University of Virginia Charlottesville, Va.	Brazil China Ghana India Mexico
Dr. Warren Johnson	Cornell University Medical College New York, N.Y.	Brazil Haiti
Dr. James Kazura	Case Western Reserve University Cleveland, Ohio	Kenya New Guinea
Dr. Larry Laughlin	Uniformed Services University of the Health Sciences Bethesda, Md.	Brazil Peru
Dr. Myron Levine	University of Maryland Baltimore, Md.	Chile Georgia Mali
Dr. Dale Morse	New York State Department of Health Albany, N.Y.	Czech Republic Georgia Hungary Lithuania Poland Russia
Dr. Lee Riley	University of California, Berkeley Berkeley, Calif.	Bolivia Brazil Ecuador Guatemala Mexico Nicaragua Peru
Dr. Peter Small	Stanford University School of Medicine Stanford, Calif.	Mexico
Dr. Andrew Spielman	Harvard School of Public Health Boston, Mass.	Brazil Ethiopia
Dr. Ken Stuart	University of Washington Seattle, Wash.	India Indonesia Kenya Mexico
Dr. Terrie Taylor	Michigan State University East Lansing, Mich.	Malawi
Dr. David Walker	University of Texas School of Medicine Galveston, Tex.	Mexico Peru

A collaboration between scientists at Cornell University Medical Center, Ithaca, New York, and Brazilian researchers, primarily from the Medical School of the Federal University of Rio de Janeiro, has focused on the development and training of a multidisciplinary team to address issues related to tu-

TABLE III-9.

Scholars-in-Residence Program, 228 Awards by Country/Area and Region, Fiscal Years 1969–1998

Americas		Europe		Asia/Oceania		Middle East		Africa	
Country	**No. of Awards**	**Country**	**No. of Awards**	**Country/Area**	**No. of Awards**	**Country**	**No. of Awards**	**Country**	**No. of Awards**
United States	61	United Kingdom	21	Japan	15	Israel	36	Nigeria	1
Brazil	2	Sweden	20	Australia	6				
Canada	3	Germany	15	India	6				
Chile	1	Italy	10	China	2				
Mexico	1	France	8	Taiwan	1				
Peru	1	Switzerland	4						
		Denmark	2						
		Finland	2						
		Norway	2						
		Poland	2						
		Russia	2						
		Austria	1						
		Belgium	1						
		Hungary	1						
		The Netherlands	1						
Total	**69**		**92**		**30**		**36**		**1**
%	**30**		**40**		**13**		**16**		**(<1)**

berculosis research and disease control. The team has received in-country training on the immunopathogenesis of tuberculosis and the mechanisms of nosocomial transmission of tuberculosis, as well as advanced training in clinical epidemiology in the United States. Support from this training grant led to the establishment of a hospital-based tuberculosis control program at the Federal University of Rio de Janeiro. This program has resulted in marked improvement in adherence of patients to treatment protocols, decreased rates of PPD seroconversion, reduced mortality due to tuberculosis, and a dramatic increase in isolation of cases of potentially contagious tuberculosis.

Students from Malawi, working under the mentorship of investigators at Michigan State University, East Lansing, and the University of Malawi College of Medicine, Blantyre, analyzed clinical data from the Malawi Malaria Research Project that focuses on the pathogenesis and clinical management of severe malaria and on ecological determinants of disease in the community. The students took part in an entomology training program under the Malawi National Malaria Control Programme and worked with Wellcome Trust Research Laboratories and the Malawi Malaria Research Project in ongoing research on the molecular biology of the cytoadherence characteristics of malarial parasites

Researchers at the University of California, Berkeley, have collaborated with researchers at the Centro Nacional de Diagnostico y Referencia, Managua, Nicaragua, on the molecular typing of *Leishmania* strains and on the discovery of a new form of leishmaniasis, atypical cutaneous leishmaniasis. The scientists discovered this atypical variation by using a new assay based on polymerase chain reaction. They developed the assay, published a report in the literature, and used the assay to analyze clinical samples and isolates in Nicaragua.

SCHOLARS-IN-RESIDENCE PROGRAM

The Scholars-in-Residence Program was established with the creation of FIC in 1968. The Executive Order creating FIC mandates "the assembly of scientists and others in the biomedical, behavioral, and related fields for discussion, study, and research relating to the development of health sciences internationally." The Program was designed to bring outstanding scholars to the NIH to promote advanced study in the health sciences. It has pursued two objectives: (1) to enhance the intellectual milieu at the NIH through the interactions of scholars and intramural scientists and (2) to conduct advanced studies of importance to biomedicine and international health.

Since 1969, 228 scientists, including several Nobel laureates, have participated in the Program (Table III-9). Most Fogarty Scholars have come from Germany, Israel, Italy, Japan, Sweden, the United Kingdom, and the United States. Scholars have worked in a wide range of scientific disciplines. Increasing numbers have pursued studies in molecular genetics, neurobiology, immunology, and developmental biology.

In FY 98, following the recommendation of an external advisory panel, administration of the Scholars-in-Residence Program was taken over by the NIH Office of Intramural Research, linking it more closely with trans-NIH and intramural activities. It will, in the future, be known as the Fogarty Scholars Program. Selected research accomplishments in FY 98 are described here.

A Fogarty Scholar from Germany continued studies on the development of T lymphocytes and, in particular, on ways to manipulate the balance between the helper T_H1 and T_H2 lymphocytes by treatment with anti-CD4 monoclonal antibodies. The purpose of this work is to discover the in vivo mechanisms that drive lymphocyte differentiation, a vital process in the development of the immune system.

An Italian Fogarty Scholar's research built on his earlier work, which suggested that the *ret* oncogene may be a causative agent of thyroid papillary carcinomas. This finding raises the possibility of a new treatment. The approach has been to construct immunotoxins carrying specific antitumor activity against the medullary thyroid carcinomas of the thyroid gland. To do this, investigators have identified antibodies that have specificity against mutated ret protein and therefore are capable of selectively killing tumor cells expressing the mutated ret form.

A Fogarty Scholar from the United States continued his collaborations with several NIH intramural scientists on glycoproteins, with emphasis on the carbohydrate moiety of these complex molecules. Such work is relevant to new avenues for vaccine development, as well as studies on the matrix substances that form the structural features of connective tissue and bone. Abnormalities in glycoproteins that are genetically inherited can result in various hereditary diseases. Additional work in this area also is needed for understanding of the complexity of three-dimensional structures and biological functions of proteins as diverse as enzymes and antibodies.

Another Fogarty Scholar from the United States conducted research on the role of nitric oxide (NO) as a risk factor for human cancers. There is extensive epidemiologic evidence that the presence of chronic infections and the accompanying inflammatory state significantly elevate the risk for certain major human cancers. This research is based on the hypothesis that DNA damage and mutagenesis resulting from long-term levels of NO produced by inflammatory cells are important factors contributing to the development of cancer. The work has potential clinical significance, because measures to diminish formation of NO in inflammatory sites of chronic disease might diminish this potential risk of cancer.

SENIOR INTERNATIONAL FELLOWSHIP PROGRAM

The Senior International Fellowship Program was established in 1975 to provide opportunities for mid- and senior-career-level U.S. scientists to undertake biomedical research studies at foreign institutions. Since the inception of the Program, more than 840 U.S. scientists have undertaken fellowships abroad, mainly in Western Europe. In FY 98, the Senior International Fellowship supported 21 investigators to undertake projects in eight countries (Table III-10). Examples of the work supported by the Senior International Fellowship Program are presented here.

A Senior International Fellow from Johns Hopkins University, Baltimore, Maryland, is working in the laboratory of a French colleague at the Institut de Génétique Moléculaire, Montpellier, to explore retroviral RNA processing and pathogenesis. The major goal is identification of regulatory elements involved in control of viral RNA splicing and in transport of viral RNA from the nucleus to the cytoplasm. By comparison of such elements from different retroviruses in the host laboratory, correlation between features of RNA metabolism and pathogenesis will be analyzed. These studies may provide new insight into the function of RNA regulatory elements in retroviruses.

A Senior International Fellow from Cornell University, Ithaca, New York, conducted research on the neurobiology of learning, in collaboration with scientists at the Fitzpatrick Institute of African Ornithology, University of Cape Town, South Africa. The acquisition of song by birds is a well-known model used to investigate the neuroanatomy of learning and the changes that take place in the brain during the learning process. This work complements the researchers' ongoing exploration of structure–function relationships in the brain. A unique focus is the study of the brains of both male and female warblers, for whom the male's song is an important part of selecting a mate.

INTERNATIONAL RESEARCH FELLOWSHIP PROGRAM

The International Research Fellowship (IRF) Program is the oldest FIC program, predating the establishment of FIC. Over its 39-year history, the IRF Program has accomplished its initial objective of helping to rebuild the science base in many European institutions after World War II and has contributed to the development of global research capacity in the biomedical sciences. The Program has proved to be effective in enabling U.S. universities to benefit from an international talent pool of postdoctoral researchers. Of equal importance, the scientific partnerships established have frequently extended beyond the duration of the award. Since its inception, more than 3,000 foreign scientists have been trained through the IRF Program. The Program was recently restructured to emphasize research training for scientists in developing countries. In FY 98, the IRF Program supported 26 postdoctoral researchers from 17 countries (Table III-11). Examples of the training supported by FIC's IRF Program are presented here.

An International Research Fellow from Poland, working in a laboratory at the Dana Farber Cancer Institute, Boston, Massachu-

TABLE III-10.

Senior International Fellowship Awards by Region and Country, Fiscal Year 1998

Region/Country	No.
Europe	
France	5
United Kingdom	5
Germany	4
Sweden	2
The Netherlands	1
Switzerland	1
Africa	
South Africa	1
Asia, India, Middle East	
Australia	2
TOTAL	**21**

TABLE III-11.

International Research Fellowship Awards by Region and Country, Fiscal Year 1998

Region/Country	No.
Central and Eastern Europe	
Poland	5
Hungary	3
Greece	2
Armenia	1
Belarus	1
Bulgaria	1
Czech Republic	1
Romania	1
Latin America	
Argentina	2
Mexico	2
Brazil	1
Chile	1
Venezuela	1
Asia and Middle East	
Thailand	1
Turkey	1
Africa	
Nigeria	1
Zimbabwe	1
TOTAL	**26**

TABLE III-12.

Minority International Research Training Grants, Fiscal Year 1998

Principal Investigators	U.S. Institutions	Collaborating Countries
Dr. L. Adams-Campbell	Howard University Cancer Center	Cameroon, Jamaica, South Africa, Zimbabwe
Dr. Winston Anderson	Howard University	Ethiopia, Italy, Mali, Nigeria
Dr. Ernestine Baker	University of Maryland, Baltimore	England
Ms. Carol Bender	University of Arizona	Argentina, Australia, Brazil, Canada, Chile, Costa Rica, Czech Republic, England, France, Germany, Italy, Japan, Mexico, the Netherlands, Scotland, South Africa, Spain, Sweden
Dr. William Boto	City College of City University of New York	Uganda
Dr. Isabella Finklestein	Clark Atlanta University	Finland
Dr. John Karen Frei	Barry University	Argentina, Italy, Jamaica
Dr. Osman M. Galal	University of California, Los Angeles	Egypt, Kenya, Philippines, Thailand
Dr. Robert Glew	University of New Mexico	Nigeria
Dr. Ephram T. Gwebu	Oakwood College	Zimbabwe
Dr. John D. Hamilton	Duke University Medical Center	Brazil, Colombia, Costa Rica, Ghana, Hungary, Slovakia, Tanzania
Dr. George Hillyer	University of Puerto Rico	England, Italy, Spain
Dr. Pauline Jolly	University of Alabama, Birmingham	Bangladesh, Guatemala, Jamaica, Peru, Zambia
Dr. Ora Lockley	Albany State University	Canada, Germany
Dr. Steven Lopez	University of California, Los Angeles	Mexico
Dr. Betsy Lozoff	University of Michigan	Bolivia, Chile, China, South Africa
Dr. B. J. McElmurry	University of Illinois, Chicago	Botswana, Colombia, Swaziland
Dr. D. Onolemhemhen	Wayne State University	Ghana
Dr. Susan Opava	California Polytechnic State University	Czech Republic, England, France, Germany, Guatemala, Spain
Dr. Charles L. Ortiz	University of California, Santa Cruz	Argentina, Mexico
Dr. E. A. Petropoulos	Michigan State University	Brazil, Bulgaria, Thailand
Dr. Robert S. Pozos	San Diego State University	Germany, Mexico
Dr. Eloy Rodriguez	Cornell University	Dominica, Dominican Republic, Uganda, Venezuela
Dr. Raymond F. Sis	Texas A&M University	Mexico
Dr. Thomas B. Smith	San Francisco State University	Cameroon, Mexico
Dr. George B. Stefano	SUNY/College at Old Westbury	China, France, Italy
Dr. Marilyn Sutton-Haywood	Johnson C. Smith University	Australia
Dr. Kim Tan	Winston-Salem State University	Finland, Singapore
Dr. Eugene S. Tull	University of Pittsburgh	Barbados, Trinidad and Tobago
Dr. Isai T. Urasa	Hampton University	Tanzania
Dr. Louis P. Villarreal	University of California, Irvine	Spain
Dr. Jordan Warnick	University of Maryland	Israel, the Netherlands
Dr. Bruce H. Weber	California State University, Fullerton	England
Dr. Michelle Williams	University of Washington	Ecuador, Peru, Zimbabwe
Dr. Saul Winegrad	University of Pennsylvania	Belgium, Botswana, France, Ghana, Japan, Scotland

setts, demonstrated that multiple genes are associated with the inheritance of a rare congenital (Diamond-Blackfan) anemia. The investigator mapped the location of these genes on human chromosomes.

An International Research Fellow from Poland, working at the Mayo Clinic, Rochester, Minnesota, established a model system for studying rheumatoid arthritis by transplanting human joint lesions into immunodeficient mice, to determine the specific human immune cell populations that regulate the development of pathology in joint tissue.

An International Research Fellow from Turkey, working with a scientist at Duke University, Durham, North Carolina, identified specific neurons involved in the transmission of information from the retina of the eye to the region of the brain that processes visual–motor signals and coordinates rapid eye movement responses to follow an image.

MINORITY INTERNATIONAL RESEARCH TRAINING PROGRAM

In cooperation with the NIH Office of Research on Minority Health, FIC established the Minority International Research Training (MIRT) Program in FY 93 to provide international educational and research training opportunities to minorities underrepresented in the scientific professions. Training grants are provided to U.S. colleges and universities to stimulate students to pursue biomedical research careers through international experiences. Support is also provided for faculty members to conduct collaborative international research and to serve as mentors to students abroad.

The MIRT Program is intended to cultivate qualities of leadership by broadening intellectual and cultural horizons. The Program strives to ensure equal opportunity by creating and expanding programs for minority students and scientists to study abroad. An additional objective is to help ensure that the full diversity of the U.S. student population is represented abroad by young diplomats of science.

The MIRT Program incorporates consortium awards that include partnerships between minority and majority institutions. Long-term objectives of these consortia are to increase cooperation between minority and majority institutions and to strengthen an important educational pipeline by exposing students who attend 2- and 4-year minority institutions to major research universities.

In FY 98, 35 MIRT programs were active at colleges and universities throughout the United States. An additional 44 colleges and universities participated as members of consortia. MIRT programs spanned more than 50 countries (Table III-12). Since implementation of the MIRT Program, more than 1,200 students and faculty have participated. Minority students and faculty who are not associated with grantee institutions or consortia may apply to participate in a particular international research program. Examples of MIRT projects are presented here.

Howard University, Washington, D.C., focused its efforts on several African nations. Notably, students provided technical assistance in studies to discover the genetic and environmental determinants of non–insulin-dependent (type 2) diabetes mellitus. Type 2 diabetes is unusually prevalent in West Africa, affording opportunities to examine patterns of DNA inheritance. Students also investigated traditional medicine practices for the treatment of diabetic conditions in West Africa.

Students from the University of Maryland, Baltimore, worked at the Federal University of Rio de Janeiro, Brazil, on the biophysics of excitable tissue, using the electric eel as the experimental model. Students also worked at the Center for Vaccine Development, Santiago, Chile, on a range of activities, from inpatient volunteer surveys to large-scale trials, and they did preparatory course work on research ethics.

Albany State University, New York, worked with the Max Delbruck Center for Molecular Medicine, Berlin, Germany, conducting experimental studies on causes of hypertension and hypertensive conditions related to organ damage. The researchers explored the biology and function of peptide systems involved in cardiovascular regulation. At Italy's University of Cagliari, students examined liver regeneration at specific stages after surgery and studied tumor cell biology related to liver cancer.

Michigan State University, East Lansing, cooperated with Chiang Mai University, Thailand, on antimicrobial resistance to selected pathogens in farming communities in northern Thailand. Also, studies were pursued at the University of the Philippines to characterize the genetic components of a strain of *Schistosoma mansoni* that is endemic in the Philippines. The goal of this research was to develop immunization strategies for preventive vaccines.

INTERNATIONAL RELATIONS

FIC-Department of State Cooperation

FIC promotes international collaboration among scientists through development and administration of international agreements and policy initiatives and through facilitation of information exchange and establishment of informal mechanisms of cooperation. FIC serves as the NIH focal point for the U.S. Department of State and international components of other Federal agencies, international organizations, and foreign governments, as well as other partners, including nongovernmental organizations.

Joint Fund and Special Foreign Currency Programs

Central and Eastern Europe

FY 98 marked the end of several Joint Board programs with Central and Eastern European countries. To facilitate the transition to more traditional sources of research support, the Department of State organized a delegation of U.S. science and technology agencies to visit Croatia, the Czech Republic, Hungary, Slovakia, and Slovenia, in April 1998. A number of U.S. Government agencies participated. The NIH was represented by staff from FIC and the Center for Scientific Review. The purpose of the visits was to exchange information with counterpart organizations and scientists on opportunities for support for scientific and technological research and training.

The Joint Boards for the Hungarian and Polish Joint Funds met in May and September 1998, respectively. The U.S.-Polish Joint Board meeting marked the last round of awards for the U.S.-Poland Joint Fund, which granted 5 of 11 new awards in health research. The U.S.-Hungary Joint Board made no new awards. FIC will continue to assist in the monitoring and follow-up of awards in the biomedical research area during the final phases of these programs.

Egypt

Under a U.S.-Egypt Science and Technology Agreement signed in 1995, the Department of State and the Ministry of Higher Education and Scientific Research in Egypt provides funds for activities of the U.S.-Egypt Joint Science and Technology Board. In FY 98, FIC coordinated the scientific review of proposals for the joint U.S.-Egypt biotechnology projects under the U.S.-Egypt Science and Technology Agreement. Six projects were chosen for support at a meeting of the U.S.-Egypt Joint Science and Technology Board, in Cairo, on June 18, 1998. In addition, the joint board approved a new program to support short-term travel awards to U.S. investigators seeking to develop new collaborations in biotechnology with Egyptian partners. Through this FIC-administered program, 13 travel grants were awarded to six NIH investigators and seven extramural scientists.

U.S.-India Fund

FY 98 marked the end of the U.S.-India Fund. In the last allocation of funds, awards were made for 12 new projects, and six ongoing projects were extended. The equivalent of approximately $1.4 million in U.S.-owned rupees was allocated to teams of U.S. and Indian biomedical researchers.

Spain

In FY 98, the U.S.-Spain Joint Science and Technology Board granted the first awards under the new U.S.-Spain Joint Science and Technology Fund. FIC coordinated the review of approximately 80 applications in the life sciences, and 11 awards were made at the joint board meeting in Madrid, on March 16–17, 1998.

Department of State Document on HIV/AIDS

Working closely with the NIH Office of AIDS Research and NIH Institutes and Centers, FIC coordinated the development of NIH input into the Department of State document entitled U.S. International Response to HIV/AIDS. The document will assist U.S. diplomats in articulating priorities of technical agencies for combating HIV/AIDS globally.

Binational Commissions

FIC coordinates NIH activities under a range of binational commissions chaired by the vice president of the United States and his counterparts in other countries.

Russia

The NIH participates in two committees under the U.S.-Russia Commission on Economic and Technological Cooperation. Within the Health Committee, NHLBI, NIAID, NICHD, and NIDA identify priority activities that would benefit from joint efforts. Areas of focus include health education and health promotion (e.g., prevention of cardiovascular disease and drug and alcohol abuse); treatment and control of infectious diseases; and maternal and child health. In FY 97, new collaborations began in the areas of micronutrient deficiency, mental health, and communications, under the leadership of NIDR, NIMH, and the National Library of Medicine, respectively. NIH activities in the Science Committee have been limited largely to joint efforts with the U.S. Civilian Research and Defense Foundation (CRDF), which is described later in this section. FIC coordinates NIH efforts under both the Health Committee and the Science Committee.

South Africa

The Health Working Group of the Gore-Mbeki Binational Commission held meetings in Pretoria, South Africa, on February 25–27, 1998, to discuss ongoing joint activities and new opportunities for joint efforts. FIC, along with staff from the National Institute on Alcohol Abuse and Alcoholism, NIAID, and NIMH, made presentations on ongoing NIH-supported initiatives in emerging infectious diseases and research on mental health services and on fetal alcohol syndrome. FIC serves as the NIH focal point for coordination of medical research activities under the Gore-Mbeki Binational Commission and works to provide information to South African researchers and institutions on an array of opportunities for joint research efforts.

Ukraine

FIC has represented the NIH in the U.S.-Ukraine Science and Technology Working Group of the Gore-Kuchma Commission since its first meeting in November 1996. Within the framework of the interagency working group's objectives is the promotion of cooperation in science and technology, including biomedical research, through facilitation primarily by CRDF and the Science and Technology Center of Ukraine. In addition, the working group provides a forum for ongoing exchange and dissemination of information on programs in the United States and Ukraine, research capabilities, government priorities, and opportunities for collaboration. NCI, NIEHS, and NIMH have been active participants in this forum. Areas of collaboration have focused on the health effects of the 1986 nuclear power plant accident at Chernobyl, Ukraine.

Other Bilateral Activities

European Union

In December 1997, the U.S. Department of State and the European Union signed the European Union-U.S. Science and Technology Agreement. As one of the first activities under the agreement, the National Academy of Sciences convened a conference entitled New Vistas in Trans-Atlantic Scientific and Technological Cooperation, in June 1998. FIC participated in the negotiation of the agreement and in the organization of the conference. FIC will continue to work with the NIH and NIH-funded scientists in developing new programs in science and technology.

Argentina

The Secretary of the U.S. Department of Health and Human Services (DHHS) signed a statement of collaboration with Argentina at the end of September 1998. This statement outlines a general framework for potential collaboration and strengthens the relationship between DHHS and the Argentinean Ministry of Health and Social Action.

Brazil

The Secretary of DHHS and her counterpart signed a broad U.S.-Brazil Health Agreement during the 1998 World Health Assembly. A Ministry of Health official visited FIC in September 1998 to discuss areas of possible strengthened collaboration under the agreement. Discussions focused on infectious diseases and protection of human subjects in medical research.

Germany

In February 1998, the Secretary of DHHS and the German Minister for Research, Education, and Technology renewed a longstanding agreement for cooperation in biomedical research. This agreement will enable the continuation of a large number of research projects in a variety of biomedical research areas, including HIV/AIDS, cardiovascular and pulmonary disease, and cellular and molecular biology.

Iceland

In September 1998, FIC participated at the U.S.-Iceland Science Day, a 1-day conference in Reykjavik to promote U.S.-Iceland scientific cooperation. Several site visits were made in conjunction with the visit.

Israel

The Director of FIC is a technical advisor to the U.S.-Israel Science and Technology Commission. The commission was established in 1994 to promote cooperative science and technology activities between the United States and Israel that could benefit the high-technology commercial sectors of both countries. The commission has the following objectives:

1. to encourage high-technology industries in the United States and Israel to undertake joint projects that will benefit both countries;
2. to encourage scientific exchanges between universities and research institutions in the United States and Israel that could lead to cooperative commercial activities;
3. to promote the development of technologies in areas including agriculture, environment, energy, information processing, microelectronics, and telecommunications, as well as medical biotechnologies; and
4. to assist, where appropriate, in the adaptation of military technology for civilian uses.

Japan

To increase the benefits of international exchange with Japan, FIC, the National Science Foundation, and the Department of Agriculture continued to support the Summer Institute Program in Japan. This program provides opportunities for U.S. doctoral candidates to gain exposure to the Japanese research environment, language, and culture, with the expectation that the participants will establish professional associations that will later assist scientific collaboration.

FIC supported 10 predoctoral life science students in FY 98, its 7th year of participation in the Summer Institute. Host institutions in Japan include universities and government and industrial research laboratories. FIC also works with the Japan Society for the Promotion of Science and the Japanese Science and Technology Agency to encourage U.S. scientists to apply for short- and long-term postdoctoral fellowships to conduct studies in laboratories of Japanese government research institutes and public corporations.

Mexico

Seven Pan American Fellows participated in the 1998–1999 U.S.-Mexico Cooperative Biomedical and Behavioral Research Program. Five of these postdoctoral fellows were placed in NIH intramural laboratories, and two were placed in extramural laboratories, for research experience in cancer, reproductive health, infectious diseases, and neuroscience. Under this program, fellows are jointly supported by NIH laboratories and the National Commission for Scientific and Technological Research of Mexico.

MULTILATERAL ACTIVITIES

U.S. Civilian Research and Development Foundation

In FY 96, the NIH contributed $1 million to CRDF to develop a new program for competitive grants. These funds were made available through FIC participation during FY 96 and supplemental funding from the U.S. Department of Defense and the government of Ukraine. On the basis of this award, CRDF announced a Biomedical and Behavioral Sciences Program to support collaborative research projects between NIH-supported U.S. investigators and their colleagues in the Newly Independent States of the Former Soviet Union (NIS). CRDF provided 20 awards for travel and workshops to enable U.S. and NIS researchers to meet and develop joint proposals for the CRDF Competitive Grants Program. Workshop topics included emerging and reemerging infectious diseases, hypertension, clinical psychiatry, aging, and alcohol abuse. In FY 97, CRDF received more than 350 proposals and granted 41 competitive awards to U.S.-NIS scientist teams. These grants totaled $1.5 million, at an average award level of $40,000 for a 2-year period. The NIS teams included 32 in Russia, 5 in Ukraine, 3 in Georgia, and 1 in Kazakhstan. At least 80% of each award directly supports NIS team expenses, including salary, travel, equipment, and supplies.

Subsequently, six NIH Institutes or Centers extended additional funding of nearly $300,000 to support several unfunded but meritorious proposals or to supplement existing CRDF awards. CRDF also received additional funds from the Department of State to support a special initiative to provide civilian research opportunities for former defense scientists in Kazakhstan.

G8 Countries

FIC coordinates with NIH Institutes and Centers, the White House Office of Science and Technology Policy, and interagency partners to develop health and science items for consideration at the annual meeting of leaders of the G8 countries: Canada, France, Germany, Italy, Japan, Russia, the United Kingdom, and the United States. In 1998, the leaders committed to increasing cooperation on emerging infectious diseases, in particular, parasitic diseases.

Human Frontier Science Program

The Human Frontier Science Program, based in Strasbourg, France, supports international grants and fellowships for basic research on the brain and cellular biology. This program was announced by the Japanese Prime Minister at the Economic Summit of the G7 nations in 1987. The program was developed and implemented in coordination with the G7 countries in 1989. All the G7 countries contribute to the program, along with Switzerland and the European Union, but Japan remains the largest contributor. The NIH contributes annually to the Human Frontier Science Program, and FIC makes the largest contribution. Examples of current multilateral research projects funded by this program are presented here.

An international team of scientists from Austria, France, Germany, Japan, and the United States is investigating the structure of the family of viruses that cause tick-borne encephalitis, dengue, Japanese encephalitis, and yellow fever. The researchers have used a combination of x-ray crystallography, cryoelectron microscopy, biochemistry, and mutagenesis to study E-protein, a protein on the viral surface. They have characterized the organization of E-proteins on the viral surface, at microscopic high resolution, and have identified conformational changes in the E-protein that might play an important role in the mechanism of viral fusion with the host cell membranes, leading to infection.

An international team of scientists from Australia, France, Japan, and the United States is studying how a group of cells known as the "organizer function" is able to induce the differentiation of the body axis in early embryos. The investigators have identified several genes that contribute to the organizer function in mice: lim1, Otx2, and HNF-3β. Deletion of these genes in knockout mice leads to defects in the development of different tissues. When mice with different gene defects are crossed, the offspring lack more than one of these genes, allowing the investigators to study the way in which the organizer genes interact to induce embryonic development.

An international team of scientists from Canada, France, the United Kingdom, and the United States is investigating the temporal relationship between cortical brain development and human recognition of faces. By studying the reaction of babies to patterns representing the human face and by measuring very low voltage electrical fluctuations on the surface of the head, the researchers have found that a newborn baby's attraction to a human face is determined by primitive subcortical brain regions. A change in the nature of the memory of a face occurs after about 2 months of age, when cortical mechanisms have become more established and face recognition becomes more dependent on experience.

World Health Organization

FIC, working with all the NIH components, provides briefings on relevant issues to U.S. delegates for the annual meeting of the World Health Organization (WHO) (including meetings of the Executive Board and the World Health Assembly) and meetings of the Pan American Health Organization (PAHO). FIC staff represent the NIH on U.S. delegations to WHO meetings as needed and participate on WHO expert committees and panels. The NIH Deputy Director for Extramural Research represents the NIH on the WHO Advisory Committee for Health Research.

In October 1998, the NIH Director hosted the recently elected Director General of WHO at the NIH. After meeting with senior NIH officials, the Director General commented on WHO reorganization and pro-

TABLE III-13.

Visiting Program: Rank Order by Country and Area, for All Institutes of the National Institutes of Health, Fiscal Year 1998[a]

> 10 Persons		5–10 Persons		< 5 Persons	
Country/Area	**No.**	**Country**	**No.**	**Country**	**No.**
Japan	309	Denmark	10	Belarus	4
China	266	Pakistan	10	Hong Kong	4
U.S. permanent residents	218	Ukraine	10	Ireland	4
Korea	142	Austria	9	Morocco	4
Italy	128	Belgium	8	Romania	4
Canada	126	Philippines	8	Singapore	4
Germany	109	Thailand	8	Nigeria	3
India	108	Chile	7	Vietnam	3
Russia	89	Bulgaria	7	Algeria	2
France	88	Croatia	6	Cyprus	2
United Kingdom	88	New Zealand	6	Egypt	2
Spain	50	Bangladesh	5	Estonia	2
Israel	49	Colombia	5	Ethiopia	2
Australia	39	Iran	5	Iceland	2
Poland	30	Portugal	5	Jordan	2
Brazil	26			Malaysia	2
The Netherlands	25			Mali	2
Hungary	24			Peru	2
Argentina	22			Serbia	2
Taiwan	22			Sri Lanka	2
Finland	20			Venezuela	2
Slovakia	18			Albania	1
Mexico	15			Armenia	1
Turkey	15			Bosnia	1
Greece	14			Burkina Faso	1
Czech Republic	12			Congo	1
Sweden	11			Cuba	1
Switzerland	11			Fiji	1
				Georgia	1
				Jamaica	1
				Latvia	1
				Lebanon	1
				Malawi	1
				Mongolia	1
				Norway	1
				Senegal	1
				Sierra Leone	1
				Slovenia	1
				South Africa	1
				Swaziland	1
				Trinidad and Tobago	1
				Tunisia	1
				Uzbekistan	1
				Yugoslavia	1
				Zimbabwe	1

[a] Total of 2,263 persons from 88 countries includes 31 Visiting Fellows at U.S. Food and Drug Administration's Center for Biologics Evaluation and Research.

gram priorities to a general NIH audience. Whenever possible, FIC arranges visits of senior WHO officials to the NIH to discuss areas of mutual interest. In 1998, the Director of WHO's new Tobacco Free Initiative and the Executive Director of WHO's Social Change and Mental Health Cluster met with counterparts at the NIH.

FIC monitors and assists, as appropriate, with NIH participation in WHO's collaborating center effort. There are 18 collaborating centers at the NIH. In October 1998, representatives of the collaborating centers in the region of the Americas met in Washington, D.C., to discuss means to strengthen cooperation and communication among regional centers and with the broader WHO network. FIC participated in and helped to organize this effort.

NIH VISITING PROGRAM

Since 1968, FIC has provided administrative and immigration-related support for foreign scientists in intramural research laboratories at the NIH and at the Center for Biologics Evaluation and Research (CBER), of the U.S. Food and Drug Administration, principally under the NIH Visiting Program, the Special Volunteer Program, and the Guest Researcher Program.

Established in 1950, the Visiting Program brings talented foreign scientists to the NIH to work or train with senior NIH investigators. A Program participant must be invited to the NIH by a senior intramural investigator who will sponsor the visitor's research.

In FY 98, immigration-related support services were provided for 2,232 scientists at the NIH and 31 at CBER, a total of 2,263 scientists from 88 countries, under the Visiting Program. All of these fellowships were funded in full or in part by the NIH Institute in which the foreign scientist conducted the research or by CBER.

Special Volunteers and Guest Researchers are supported financially by their home institutions, foreign and domestic organizations, or both. Guest Researchers are independent scientists conducting their own research at NIH facilities. During FY 98, there were 99 Guest Researchers from 23 countries. Special Volunteers work in collaboration with and under the direction of an NIH sponsor. During FY 98, there were 523 Special Volunteers from 59 countries.

Tables III-13 through III-15 illustrate the distribution of foreign scientists by country.

INTERNATIONAL CONFERENCES, LECTURES, AND CONSULTATIONS

Another role of FIC is to bring together scientists from many parts of the world to confer and to explore health issues of worldwide significance. For these purposes, FIC supports conferences, seminars, meetings, and workshops. In addition, FIC works with international and domestic partners to develop approaches for addressing critical needs for global health and biomedical research. Some of the international meetings in FY 98 are described here.

FIC was a cosponsor of the 1st International Conference on Emerging Infectious Diseases, in Atlanta, Georgia, on March 8–11, 1998. The conference, which was organized by CDC, the Council of State and Territorial Epidemiologists, the American Society for Microbiology, and the National Foundation for CDC, was convened to address issues and concerns about emerging infectious diseases and to present recent data on this global health problem.

In collaboration with other NIH components and the University of California, San Francisco, FIC organized a workshop on HIV/AIDS Prevention Research, which was held in San Francisco, on April 17–20, 1998. The workshop, attended by approximately 200 scientists from 38 nations, presented an opportunity for scientists from industrial and developing countries (a) to review the status of available stratagems to prevent HIV transmission, by using both biomedical and behavioral interventions, and (b) to develop approaches and partnerships for future intervention studies.

An international conference on the Value of Plants, Animals, and Microbes to Human Health, in New York City, New York, on April 17–18, 1998, was organized by the American Museum of Natural History and the Center for Health and the Global Environment, Harvard Medical School, Boston, Massachusetts, and was cosponsored by FIC and the United Nations Environment Programme. The meeting focused on in-depth analysis of the historical and current contributions of diverse organisms to the discovery of new therapeutic agents; important models for medical research in bioprospecting; and health-related ecosystem functions that affect human health.

PAHO, NHLBI, and FIC sponsored a 50th-anniversary conference on Global Shifts in Disease Burden: the Cardiovascular Disease Pandemic, in Washington, D.C., in May 1998. The conference highlighted the marked increase in the burden of cardiovascular disease throughout the world and explored opportunities for intervention; stimulated international action to address the pandemic of cardiovascular disease; and celebrated the 50th anniversary of NHLBI and WHO as an occasion to promote collaboration.

TABLE III-14.

Guest Researchers: Rank Order by Country and Area, for All Institutes of the National Institutes of Health, Fiscal Year 1998[a]

> 10 Persons		5–10 Persons		< 5 Persons	
Country	**No.**	**Country**	**No.**	**Country/Area**	**No.**
Japan	27	Italy	10	Spain	4
Germany	11	Brazil	8	United Kingdom	3
		Korea	8	France	2
		China	6	Israel	2
		The Netherlands	5	Taiwan	2
				Austria	1
				Colombia	1
				Czech Republic	1
				Denmark	1
				Egypt	1
				Greece	1
				India	1
				Jordan	1
				Macedonia	1
				Mexico	1
				Poland	1

[a] Total of 99 persons from 23 countries.

TABLE III-15.

Special Volunteers: Rank Order by Country and Area, for All Institutes of the National Institutes of Health, Fiscal Year 1998[a]

> 10 Persons		5–10 Persons		< 5 Persons	
Country	**No.**	**Country**	**No.**	**Country/Area**	**No.**
Japan	111	Italy	10	Spain	4
Germany	65	Brazil	8	United Kingdom	3
China	38	Korea	8	France	2
Italy	30	China	6	Israel	2
Korea	30	The Netherlands	5	Taiwan	2
United Kingdom	21			Austria	1
				Colombia	1
				Czech Republic	1
				Denmark	1
				Egypt	1
				Greece	1
				India	1
				Jordan	1
				Macedonia	1
				Mexico	1
				Poland	1

[a] Total of 356 persons from 27 countries.

IV.
National Institute on Aging

INTRODUCTION

The National Institute on Aging (NIA) conducts and supports biomedical, social, and behavioral research, training, dissemination of health information, and other programs that address the aging process and the diseases, special problems, and needs of the aged. NIA research priorities include Alzheimer's disease; the aging process; frailty, disability, and rehabilitation; health and effective functioning; and long-term care.

NIA awards grants to research institutions through extramural grant programs—the Behavioral and Social Research Program, the Biology of Aging Program, the Geriatrics Program, and the Neuroscience and Neuropsychology of Aging Program. In addition, scientists conduct intramural research through the Epidemiology, Demography, and Biometry Program and the Intramural Research Laboratory Program.

The NIA Office of International Activities coordinates international activities under bilateral, multilateral, and other agreements and works with NIA scientists to develop an overall strategy to advance the NIA mission in international research on aging.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

The Office of Demography of Aging (ODA) helped to draft the communiqué for the Denver G8 Summit Meeting in May–June 1997. ODA's major contributions were to highlight current research issues related to population aging, projections, retirement, disability trends, and cross-national research opportunities and to stress the need for appropriate and comparable data. The last paragraph of the final communiqué on population aging reflects the success of ODA in these efforts:

> We agreed that it is important to learn from one another how our policies and programs can promote active aging and advance structural reforms to preserve and strengthen our pension, health, and long-term care systems. Our governments will work together, within the OECD [Organization for Economic Cooperation and Development] and with other international organizations, to promote active aging through information exchanges and cross-national research. We encourage collaborative biomedical and behavioral research to improve active life expectancy and reduce disability and have directed our officials to identify gaps in our knowledge and explore developing comparable data in our nations to improve our capacity to address the challenges of population aging into the 21st century.

This language has acted as a powerful catalyst and has spurred several international organizations and some national governments to make research on population aging a higher priority in their agendas.

An investigator at McGill University, Montreal, Quebec, who is supported by the Biology of Aging Program (BAP), is using a unique set of immunoreagents to examine age-related changes in the extracellular matrix of human articular cartilage, by looking for alterations in degradation of type II collagen. Fibrils containing type II collagen provide the tensile properties of cartilage and its molecular integrity. An understanding of how molecular damage to collagen occurs could lead to new therapeutic means of preventing changes that lead to loss of joint function. By comparing cartilage isolated from diseased and healthy age-matched knee (a common site for osteoarthritis) and age-matched ankle (a rare site for osteoarthritis), this investigator is attempting to determine whether there is a similarity in changes in aging and osteoarthritis.

Staff from the Epidemiology, Demography, and Biometry (EDB) Program and Japanese investigators have been involved in a series of studies, collectively called the Ni-Hon-Sea Study, to identify whether rates and causes of dementia are the same or different across cultures. If the rates are different, efforts will be made to discover modifiable risk factors. A report published in the *Journal of Gerontology* in July 1998 describes the standardization of procedures, particularly for detection and diagnosis of dementia, which resulted from the cross-cultural cross-national study of older adult Japanese in Hiroshima and Tokyo (Ni), Japan; Honolulu (Hon), Hawaii; and Seattle (Sea), Washington. Such standardization is essential for making valid and meaningful comparisons of rates and patterns of dementia across sites and will facilitate the study of genetic and environmental risk factors for dementia among migrating ethnic populations.

A Postdoctoral Fellow from Ajou University Hospital, Suwon, Korea, was awarded the Glenn Foundation Endocrinology and Aging Award, in June 1998, for research conducted through the NIA Intramural Laboratory Research Program. The investigator studied the expression of DNA repair enzymes under the control of hormonal and growth factor stimulation. This research has shown that insulin is a survival factor in cells partly because it increases levels of DNA repair enzymes.

The Neuroscience and Neuropsychology of Aging (NNA) Program supported collaboration between investigators from the University of Colorado Health Sciences Center, Denver, and the Karolinska Institute, Stockholm, Sweden, which provided insights into neuronal survival and maintenance of neural circuits throughout life. The researchers mapped the pattern of gene expression for two related neurotrophic factors (neurturin and neurotrophic factor derived from a glial cell line) and for specific receptor proteins for these factors in the developing and adult nervous system of rodents. Findings suggested multiple independent and overlapping roles for these two neurotrophic factors in the developing and adult organism. Continued exploration of the synthesis, localization, and biological effects of these factors and their receptor molecules in the adult and aging nervous system will contribute to understanding of the role of such factors in health and disease and will guide development of treatment strategies based on neurotrophic factors.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Germany

The NNA Program sponsored a workshop on Neuroimaging and Biological Markers in Early Diagnosis and Monitoring the Course of Alzheimer's Disease, on June 15–16, 1998. This workshop was carried out as part of the U.S.-German Cooperation in Health Research that is a joint initiative of NIA and the Federal Ministry for Education, Sciences, Research, and Technology. The meeting is the latest in a series of workshops to bring together U.S. and German scientists from both basic and clinical disciplines to exchange information on selected topics about Alzheimer's disease and to stimulate bilateral scientific cooperation in research. Discussions at this workshop explored the potential usefulness of various biological markers and neuroimaging methods for early diagnosis of Alzheimer's disease and for monitoring the course of the disease.

Italy

The EDB Program collaborated with the Aging Project of the Veneto Region (Progetto Veneto Anziani [PROVA] Study) of Italy, on an observational study designed to depict the causal pathway from disease to disability in a representative group of older Italian men and women. This study had a special focus on the synergism between cardiovascular and osteoarticular disease. The study population consists of 3,000 men and women age 65 years or older from the towns of Camposampiero and Rovigo, near Padua. An EDB Program investigator developed study protocols in collaboration with PROVA study investigators and trained examiners to perform physical assessments and performance measures of functioning.

Both the EDB Program and the National Institute of Neurological Disorders and Stroke are collaborating with the Italian National Institute for Research and Care of the Elderly. The joint study is conducted under the auspices of the U.S.-Italy Science and Technology Agreement on the Postural Control in the Elderly Study, Ospedale I Fraticini, Geriatrics Department, Florence. This study will develop measures that identify specific components of balance problems and then evaluate how these components contribute to the problems. A pilot study of reliability of the performance-based tests has been completed. An EDB Program investigator provided consultation on development of the testing instruments and will collaborate on data analysis.

EDB Program investigators continue collaboration on the Italian Longitudinal Study on Aging (ILSA), carried out as part of the Target Project on Aging of the National Research Council of Italy. ILSA started in 1991 and has already completed two follow-ups of a nationally representative cohort of 5,600 individuals who are 65–84 years old . Investigators are assessing the health status, the transition in physical and cognitive functioning with age, and the biological, socioeconomic, and environmental determinants of healthy aging.

Activities With International and Multinational Organizations

ODA supported an interagency agreement with the Office of International and Refugee Health to continue a cross-national statistical and mathematical modeling project at the World Health Organization (WHO). There have been two main activities. First, ODA provided funds (1) to assemble data on active life expectancy (years of expected life free of serious disability) and on risk factors for chronic disease and (2) to develop microdata-based mathematical models of chronic disease, disability, survival, and the use of home health care. In October 1997, ODA sponsored a meeting to integrate these microdata-based approaches to projecting health and disability with the macrodata-based approach used in the report, *The Global Burden of Disease,* which was authored by the United Nations, WHO, and the Harvard School of Public Health, Boston, Massachusetts. This meeting resulted in a report entitled Forecasting Morbidity, Mortality, and Disability in Noncommunicable Diseases.

Second, ODA supported the preparation of data for a cross-national analysis of the need for home and community care based on national surveys of limitations of both physical and psychological function. The main activity has been attempts to harmonize data sets by using a multivariate filtering system, so that similar home care needs can be distinguished across surveys with nonoverlapping domains of survey questions. ODA is also supporting WHO in efforts to project the global burden of diabetes, including estimation of the number of persons with the major long-term complications of diabetes.

Through a contract with the National Academy of Sciences, ODA is supporting the development of a global research agenda for population aging. The main focus of this effort will be populations in industrial nations, but the research agenda will also include a focus on developing countries.

Through the U.S. Bureau of the Census, ODA supports the Population Activities Unit of the United Nations-Economic Commission for Europe, in Geneva, Switzerland; OECD; and the United Nations Population Division. Through the interagency agreement, ODA supported (1) the collection, standardization, and archiving of the microdata from a large number of industrial countries; (2) publication of the *Directory of Population Aging Research in Europe;* and (3) preparation of a Report on Aging Research in Europe: Demographic, Social, and Behavioral Aspects, containing detailed information on large-scale, nationally representative research efforts. (Until very recently, the United States was virtually the only country making census microdata available to the public.) Through the interagency agreement with OECD, ODA is supporting international comparisons of treatments for a spectrum of prevalent conditions in the older population with high aggregate medical expenditure. ODA also supported the report on Maintaining Prosperity in an Aging Society. Through the interagency agreement with the United Nations Population Division, ODA is supporting population estimates and projections for 5-year age groups up to age 100 years. (Until now, such detail was available only up to 80 years of age, with a final open-ended category of age 80 years or older.)

Extramural Programs

Behavioral and Social Research Program

The Behavioral and Social Research Program supports social and behavioral research and training on aging processes and the place of older people in society. The Program's international activities emphasize demographic research studies of health and productive functioning in the middle and later years of life and the delivery of services in the various cultures. The focus of these studies includes the work, health, and family responsibilities of men and women approaching retirement, as well as the cognitive functioning of older persons.

The Adult Psychological Development Cluster supports the cooperative behavior genetics projects of Pennsylvania State University, University Park, with two Swedish institutions: the Institute of Gerontology, Jönköping, and the Karolinska Institute, Stockholm. Both projects involve longitudinal studies with samples of older Swedish twins reared together and apart. These studies focus on many factors, but primarily on the contributions of heredity and environment to cognitive functioning, health, personality, and interpersonal relationships. The Adult Psychological Development Cluster also supports the Victoria Longitudinal Study conducted by the University of Victoria, British Columbia. This longitudinal study investigates cognitive functioning in older adults.

The Demography and Population Epidemiology (DPE) Cluster funds or cofunds several international data collection and analytic research efforts. Data collection and archiving studies funded by these grants include (a) a study on population aging in Asia (the Philippines, Singapore, Thailand, and Taiwan); (b) surveys in Bangladesh, Indonesia, South Africa, Thailand, and Vietnam; (c) research to develop standardized measures within the Luxembourg Income Study database (Belgium); and (d) development and archiving of the German equivalent of the Michigan Panel Study of Income Dynamics. Completed grant projects include surveys of the oldest-old in Australia and Israel and a follow-up of the Malaysian Family Life Survey.

DPE Cluster grant projects for analytic research include a study of how pension and tax policies affect participation in the labor force across a number of industrial countries. Investigators found that what might be called in effect "a tax on older workers" (age 60 years or older) has a massive impact on discouraging their participation in the labor force, especially in countries such as Belgium, France, and Italy. The findings from this study have had considerable impact on research and policy in a number of European countries.

Other investigators, in an effort to describe and explain mortality patterns at age 80 years or older, are collecting and analyzing comparative and historical demographic data from several European countries, including Denmark and Sweden, which have better data on vital statistics than the United States does.

The DPE Cluster supports small grant awards focused on study of older adults in China and Vietnam; changes in adult mortality resulting from alterations in health insurance coverage in Costa Rica; and the pension system in South Africa. Through R13 conference grants, the DPE Cluster also supported several of the Réseau Esperance de Vie en Santé (REVES) meetings on active life expectancy, as well as a conference on International Health and Retirement Surveys.

ODA supported the publication of a wall chart, "Global Aging Into the 21st Century"; a comparative international chartbook, *Older Workers, Retirement, and Pensions;* an international brief, *Old Age Security Reform in China;* and a revision of an international population report, *An Aging World II,* prepared by the Center for International Research, Bureau of the Census. The international population report is being revised, and publication is expected to coincide with the International Year of the Older Person—1999. ODA also supports an interagency agreement with the Office of International and Refugee Health and WHO, providing funds for a cross-national statistical and mathematical modeling project. (See also the section on "Activities With International and Multinational Organizations.")

ODA helped to draft the communiqué for the Denver G8 Summit Meeting. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

Biology of Aging Program

BAP supports studies on the biomarkers of aging, cell biology, endocrinology, pathobiology, physiology, genetics, immunology, molecular biology, and nutrition and metabolism. The Program also supports facilities that provide investigators with aging animals and cell cultures for use in research.

BAP-supported research at Prince Henry's Institute for Medical Research, Victoria, Australia, explored the physiological function of local estrogen biosynthesis in bone and adipose tissue. Understanding these processes is essential to elucidating the role of estrogen in health changes in older adults. This laboratory also developed a unique transgenic mouse strain lacking estrogen biosynthesis. That accomplishment, together with biochemical studies and modification of the transgenic mouse strains to make the transgene expression tissue selective, will allow these studies to proceed.

In addition, BAP supported research on fibroblasts, growth control, aging, and programmed cell death (apoptosis), by an investigator at Lady Davis Institute for Medical Research, Sir Mortimer B. Davis Jewish General Hospital, Montreal. The investigator has identified two proteins: statin and terminin. A direct relationship between the level of expression of statin and long-term survival has been found in patients with breast cancer, suggesting that statin is a marker of cell proliferation. This finding can be important in the characterization of human breast and colon cancers. The processing of the protein terminin appears to be a molecular marker of an early step in apoptosis. This research is highly relevant to the NIA programs, because it promises to offer key insights into the processes of aging and cancer. The investigator will ultimately test whether cancer could be the result of a reduced ability of precancerous cells to undergo apoptosis. If this is the case, terminin may be a unique diagnostic marker for cancer.

At McGill University, Montreal, BAP also supports research on aging of the male reproductive system in rats. This research is part of a program project grant awarded to an investigator at Johns Hopkins University School of Medicine, Baltimore, Maryland. The work focuses on basic cellular and molecular research on aging of the testis, prostate, and epididymis. Results from the Montreal component of this study demonstrate remarkable age-related changes in the intracellular organization and epithelial structure of the epididymis and in the pattern and timing of epididymal gene expression related to male fertility, as well as increased sensitivity to androgen, the male steroid hormone. These results also showed effects of paternal age on fertility and on outcome for progeny. When rats of increasing age were mated with young females, the investigators observed an increase in loss before implantation of the fertilized ovum in the uterus, a significant decrease in average fetal weight, and a significant increase in neonatal deaths. They concluded that sperm quality decreased with age. Other observations included striking cellular changes in the epididymis with age, and androgen-dependent cell death in selected portions of the epididymis.

An investigator supported by BAP at McGill University is using a unique set of immunoreagents to examine age-related changes in the extracellular matrix of human articular cartilage by looking for alterations in degradation of type II collagen. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

Geriatrics Program

The NIA Geriatrics Program and the National Cancer Institute (NCI), National Institutes of Health (NIH), together with colleagues from the Institute of Health, Rome, and the National Cancer Institute, Milan, collaborated on the study of Cancer Prevalence Among Elderly Persons Aged 65 Years and Older in Italy and the United States. The feasibility of two precise and reliable statistical methods for estimating prevalence has been demonstrated. These methods are now being applied to estimating prevalence across the age spectrum, for several major tumors (e.g., breast, colorectal, and stomach cancer and non-Hodgkin's lymphoma). Preliminary findings indicate that there is a high frequency of cancer survivors who are older than 90 years of age, particularly for breast and colorectal cancers. Research reports are being prepared by the study team.

Neuroscience and Neuropsychology of Aging Program

The NNA Program supports studies of Alzheimer's disease and the structure and function of the central nervous system as it ages. The Program funds research and research training in fundamental neuroscience; integrative neurobiology; sleep disorders and biorhythms; dementias of aging; and cognition, sensory, perceptual, and motor processes.

A study at McGill University, Montreal, has the following goals: (1) to examine the mechanisms underlying the increased activity of the hypothalamic–pituitary–adrenal axis of aged, cognitively impaired rats and (2) to use antidepressant drugs to treat these impairments and to further the understanding of the mechanisms underlying the adverse effects of chronic activation of the hypothalamic–pituitary–adrenal axis.

Other investigators at McGill University are studying synaptic regrowth induced by neurotrophic factors. The findings demonstrate that, after a brain lesion, administration of a nerve growth factor stimulates regrowth of atrophied cholinergic fibers innervating the cerebral cortex. The study is also designed to investigate compensatory synaptic plasticity in the nervous system of aged animals.

The Indo-U.S. Cross-National Dementia Epidemiology Study of the University of Pittsburgh, Pennsylvania, in conjunction with the Centre for Ageing Research, New Delhi, India, is examining the distribution of and risk factors for dementing disorders among older people in Ballabgarh, a rural community in northern India.

Investigators at the University of Washington Medical Center, Seattle, are studying the epidemiology of dementia in older Japanese Americans and comparing results cross-culturally with those of ongoing studies in Honolulu, Hawaii, and Hiroshima, Japan.

A cooperative investigation at Indiana University, Indianapolis, and the University of Ibadan, Nigeria, compares the age-specific prevalence and incidence of dementia disorders, especially Alzheimer's disease, in a sample of African Americans 65 years of age or older living in Indianapolis and a sample of Nigerians 65 years of age or older living in Ibadan. This study also compares the neuropathology of aging and of Alzheimer's disease in these two groups and includes a prospective case–control study of risk factors for Alzheimer's disease.

Investigators from the University of Southern California, Los Angeles, are in partnership with investigators at the Karolinska Institute, Stockholm, and the Institute of Gerontology, Jönköping, to estimate the contribution of genes and environment in the expression of dementia in the Swedish Adoption/Twin Study of Aging. The use of monozygotic and dizygotic twin pairs offers unique opportunities for distinguishing the effect of genetic versus environmental influences in the onset of Alzheimer's disease.

The Karolinska Institute, Stockholm, and the University of Colorado Health Sciences Center, Denver, are conducting studies of neural grafts and growth factors, to find methods that may be useful in treating neurodegenerative diseases. The research has identified new neurotrophic factors, the receptors for those factors, and their functional activity in the brain. The findings support the potential use of neurotrophic factors in the treatment of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

Other joint studies at the Karolinska Institute and the University of Colorado Health Sciences Center provided insights into neuronal survival and maintenance of neural circuits throughout life. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

International Meetings

Office of International Activities

During FY 98, NIA's Office of International Activities arranged 14 international visits by scientists and public health administrators from several countries, including China, Croatia, Italy, Japan, Korea, the Netherlands, and the United Kingdom. Visitors were briefed on a variety of topics, ranging from the administrative operations of the Institute to common research interests.

Program Staff

December

At the international conference on Biomedical Aspects of Aging Research, in Venice, Italy, in December 1997, the Deputy Director, NIA, participated in a panel that discussed international funding for research on aging. At the same conference, the Associate Director, BAP, participated in the opening session and panel discussions on opportunities for international collaboration and research funding.

The Deputy Director, NIA, cochaired the 5th U.S.-Italy Science and Technology Cooperation Conference on the Prevention of Disease and Disability in the Elderly, in Venice. At this conference, senior investigators of the EDB Program presented research results and overviews from major longitudinal studies.

The Chief, Epidemiology and Demography Office, EDB Program, presented an invited lecture on evaluating the health of older populations, at geriatric grand rounds, at the Hospital of Camposampiero, Italy.

The Chief, Geriatric Epidemiology Office, EDB Program, presented an invited lecture at the University of Verona, Italy, on the scientific basis for the Health and Body Changes Study and the measures made in this study. A visit was also made to Padua, to consult on projects related to ILSA.

The Chief, Cancer Section, Geriatrics Program, was an invited speaker at a national scientific congress in Rome, sponsored by La Sapienza; Istituto Nazionale per la Ricerca sul Cancro, Genoa; and Gruppo Oncologico Multidisciplinare, Calabrese, Italy. She gave a presentation on cancer incidence and mortality in the United States, demonstrating the magnitude of the problem in persons aged 65 years or older.

February

The Associate Director, EDB Program, presented an invited lecture on risk factors for Alzheimer's disease, at a faculty meeting at the University of Trieste School of Medicine, Italy, in February 1998.

April

An NNA Program staff member presented the U.S. experience with Alzheimer's disease centers to the 5th International Geneva Springfield Symposium in Advances in Alzheimer Therapy, Geneva, Switzerland, in April 1998.

Two Italian researchers, a medical sociologist from Italy's National Cancer Institute, Milan, and a biostatistician from the Institute of Health, Rome, participated with staff from the Geriatrics Program in a work session in Bethesda, Maryland. They gave a colloquium sponsored by NCI (NIH), describing the findings from the study of Cancer Prevalence Among Elderly Persons Aged 65 Years and Older in Italy and the United States and discussed cancer in older adults and cancer survival in Europe, as shown by data from the Eurocare Study.

May

The Associate Director, BAP, convened the Annual Biomarkers of Aging Meeting, in Volterra, Italy, in May 1998. After this conference, a joint meeting of U.S. investigators (funded by BAP) and Italian investigators performing research on biomarkers of aging was held in Pisa, Italy.

BAP staff members attended the Gordon Research Conference on the Biology of Aging, in Barga, Italy. The Deputy Associate Director, BAP, then attended the Summer School on the Pathobiology of Aging, in Ancona, Italy. This summer school was supported by the European Commission and sponsored by the University of Pisa.

The Chief, Geriatric Epidemiology, EDB Program, presented a poster, Interleukin-6 and C-Reactive Protein Increases Risk of Death and Disability in High-Functioning Older People: the Iowa 65+ Rural Health Study, at the Gordon Research Conference, in Pisa. She also presented an invited lecture on paradoxical findings in risk factors for disease in old age, at a meeting of the Icelandic Geriatric Society.

The Chief, Epidemiology and Demography Office, EDB Program, presented an invited lecture on gender-specific differences in chronic disease and disability in the older population, at geriatric medicine grand rounds, at McGill University School of Medicine, Montreal. He also gave an invited presentation on research strategies to evaluate the pathway from disease to disability, at I Fraticini Hospital, Florence, Italy.

An international workshop, Radiation Therapy and Older Cancer Patients: Current Knowledge and Recommendations, was convened at the NIH, Bethesda, Maryland. The meeting, initiated by the Geriatrics Program, was cosponsored by NCI and the American College of Radiology. The objectives of the meeting were (1) to recommend strategies to advance the current knowledge base on radiation therapy in older adults and (2) to propose research opportunities for radiation therapy in older cancer patients. The research recommendations were published in the *International Journal of Radiation Oncology, Biology, and Physics,* in January 1999.

June

The Deputy Associate Director, BAP, attended the Benzon Symposium, Molecular Biology of Aging, at the Royal Danish Academy of Sciences and Letters, in Copenhagen, Denmark, in June 1998.

The Behavioral and Social Research Program arranged a meeting in Bethesda, Maryland, to identify promising areas for joint comparative behavioral research and social science research on aging, by investigators in Germany and the United States. Care of patients with Alzheimer's disease and treatment of and recovery from hip fracture were selected as promising areas for research. Special attention will be given to the influence of health care systems and doctor–patient interactions.

Scientists from the Molecular Physiology and Genetics Section (MPGS), Laboratory of Cellular and Molecular Biology (LCMB), attended a meeting of the Spanish Society of Gerontology, in Madrid, Spain, and presented a lecture on pharmacological enhancement of memory function. They also visited the University of Valencia, Spain, and presented a lecture on the same topic.

July

A BAP staff member participated in the 4th International Symposium on Neurobiology and Neuroendocrinology of Aging, in Bregenz, Austria, in July 1998.

The Associate Director, EDB Program, presented an invited lecture on head trauma in early life as a possible predictor of cognitive disability in late life, at the 6th International Conference on Alzheimer's Disease and Related Disorders, in Amsterdam, the Netherlands. Four NNA Program staff members also participated in this conference.

Scientists from MPGS, LCMB, attended the International Congress of Alzheimer's Disease, in Amsterdam, and presented a lecture on pharmacological enhancement of cognition. They also attended the 4th International Symposium on Neurobiology and Neuroendocrinology of Aging, in Bregenz, Austria, and presented a lecture on gene therapy and treatment of motor disorders.

August

Scientists from MPGS, LCMB, visited the University of Basel, Switzerland, and presented a lecture on calorie restriction in nonhuman primates, in August 1998. They also discussed current and future plans for collaborating on a project using unbiased stereology and examining neuromorphometric parameters of aging in various mouse models.

September

The Deputy Director, NIA, presented the keynote address and participated in the meetings of the European Academy of Geriatric Medicine in Sion, Switzerland, in September 1998.

Scientists from MPGS, LCMB, traveled to the University of Kyoto, Japan, to further the collaboration with colleagues there. The collaboration involves the establishment of biomarkers of aging in primates. The scientists visited the university's primate center, made a presentation on the NIA project on aging in monkeys, and outlined plans for the creation of a database on aging in primates. They also visited colleagues at the University of Nagoya's Department of Geriatrics to further joint research on the use of viral vectors to encode dopamine D2 receptor. In addition, the scientists visited the Aichi Prefecture Institute for Development Disabilities, to present a lecture and to discuss possible collaboration in research on cognitive enhancement in patients with mental retardation.

Scientists from MPGS, LCMB, helped to organize the 6th meeting of U.S. neuroscientists with the Italian Association for Research on Brain Aging, sponsored by NIA. This conference, which will focus on the Neurobiology of Aging, will include discussions of plans for meetings to be held in conjunction with the annual meeting of the Society for Neuroscience.

The Associate Director, EDB Program, traveled to Madrid, Spain, to participate in a workshop on current issues on prevention and health promotion for older adults. This workshop was sponsored by the National School of Public Health and Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland.

A staff member of the Geriatrics Program participated in the 7th Annual Meeting of the International Genetic Epidemiology Society, in Arcachon, France.

Intramural Programs and Activities

Epidemiology, Demography, and Biometry Program

The EDB Program conducts and supports research on the epidemiology of health and disease and the demographic and social factors that affect the health status of older persons. The EDB Program staff develops and analyzes data generated by contracts and obtained from other sources, including the Bureau of the Census, the National Center for Health Statistics, and other public agencies.

Intramural scientists in the EDB Program worked with investigators from Canada, England, Finland, Iceland, Italy, Japan, the Netherlands, and Puerto Rico and have organized the collaborative activities presented here.

A researcher from the Division of Geriatric Medicine, Dalhousie University, Halifax, Nova Scotia, working under a brief fellowship, used data from the Women's Health and Aging Study to examine chronic conditions responsible for severe walking disability. He also investigated self-reports on conditions that patients believe to be the cause of various aspects of a disability and on the chronological history of the disability.

A clinical senior research associate from the Department of Community Medicine, University of Cambridge, England, is spending 11 months in the Epidemiology and Demography Office. The Commonwealth Fund is sponsoring this visitor on a Harkness Fellowship focused on health policy on aging, and specifically, on the use of epidemiologic studies to inform policy in the United Kingdom and the United States.

A researcher from the University of Jyväskylä, Finland, began a 2-year fellowship. As a coinvestigator in two of the EDB Program's longitudinal studies—the Women's Health and Aging Study and the Honolulu-Asia Aging Study—she performed several analyses of physical activity, strength, and balance. It is anticipated that this investigator will return periodically to collaborate on research using data from these studies and will present findings from the studies to her Finnish colleagues and the international scientific community.

In an attempt to meet an anticipated need for new resources to study genetic susceptibility and gene–environment interaction in diseases of old age, EDB Program investigators traveled to Reykjavik, Iceland, to discuss collaboration in the Reykjavik Study. This study involves more than 30,000 people—more than one-half of the Icelandic population in the birth cohorts of 1907 through 1935.

Senior EDB Program investigators have contributed to the theoretical and developmental components of a new 1,450-subject study, the In Chianti Project, currently being conducted in the Tuscany Region of Italy. The study goals are to understand multiple risk factors that influence loss of ability to walk in older persons. The Geriatric Department, National Research Institute, is the coordinating center for the study. Collaborating institutions are the local municipalities of Greve in Chianti e Bagno a Ripoli, the Tuscany Region Health Authority, and the Institute of Gerontology, University of Florence. The study has received a grant from the Italian Ministry of Health.

A study of inflammation and heart disease in the EDB Program's Health and Body Composition (HEALTH ABC) Study was included as one of five projects that are part of the program on Heart Failure, Pathological Aging, and Disability in the Elderly Research. This project is cofunded by the Catholic University, Rome, and the Italian Ministry of Research, as part of the Programs of Relevant National Interest.

EDB Program staff and Japanese investigators have been involved in a series of studies, collectively called the Ni-Hon-Sea Study, to identify whether rates and causes of dementia are the same across cultures. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

After a 2-year fellowship in the Geriatric Epidemiology Office, a researcher returned to the Department of Human Nutrition, Wageningen Agricultural University, the Netherlands, where she was awarded a prestigious and highly competitive grant to continue her work on muscle strength and function in older persons. She is a coinvestigator on the HEALTH ABC Study.

The EDB Program has entered an agreement with the University of Puerto Rico Medical Sciences Campus, Department of Biostatistics and Epidemiology, to conduct a feasibility study for future follow-up of brothers participating in the Puerto Rico Heart Health Program. A proposed future study would focus primarily on genetic susceptibility to cognitive decline and dementia in men 80 years old or older and their siblings.

Intramural Research Laboratory Program

NIA carries out laboratory and clinical research at the Gerontology Research Center, Baltimore, Maryland, and at the Warren Grant Magnuson Clinical Center, NIH, Bethesda, Maryland. Studies at NIA focus on the basic mechanisms of aging and how basic biological changes in health and disease states differ from the normal changes occurring during the aging process. The Intramural Research Program consists of nine research laboratories and the Longitudinal Studies Section, which is also responsible for conducting the Baltimore Longitudinal Study of Aging (BLSA).

Researchers in the Laboratory of Molecular Genetics collaborated with scientists in Denmark, England, France, Germany, the Netherlands, and Slovakia on studies of DNA repair and transcription in human disorders of premature aging and in older adults. Scientists in the Laboratory work with scientists at Copenhagen University and Aarhus University, Denmark, through a collaborative organization, the Danish Center for Molecular Gerontology. The projects involve the role of topoisomerases in DNA repair, the functions of the Werner protein, and the differential expression of specific proteins in old versus young cells. Researchers in the Laboratory also participated in meetings in Asia, Europe, and the Middle East.

A Visiting Fellow recently started a 2-year appointment in the Statistical and Experimental Design Section, Research Resources Branch. She is a mathematical statistician from Canada who will be working on the development of multilevel or mixed-effects regression models for the analysis of longitudinal studies of aging.

Another Visiting Fellow from Canada is working in the Cognition Section, Laboratory of Personality and Cognition. He is a neuropsychologist who will examine the relationship among age, cortisol concentrations and hippocampal morphology in BLSA participants. In particular, he will investigate whether high cortisol concentrations are associated with reduced hippocampal volume.

The Transgenic and Knockout Facility Section, Research Resources Branch, is hosting a Visiting Fellow from Shanghai, China, in the creation of a murine conditional knockout of the μ opioid receptor via Cre-lox technology. Creation of this model is a collaborative effort to study the role of this receptor in peripheral analgesia, by scientists at the Laboratory of Cellular and Molecular Biology, National Committee on Scientific Research, Paris, France, and the Clinic of Anesthesiology, Free University of Berlin, Germany.

The Metabolism Section, LCI, is hosting two Special Volunteers from the Epidemiology Division, National Center for Longevity Sciences, Nagoya, Japan, to analyze data on the effects of body composition (e.g., obesity and the pattern of fat deposition) on classical risk factors for the development of atherosclerosis and for all-cause mortality across the entire adult life span. Discussions are under way with the Chief of the Epidemiology Division to establish comparative studies of U.S. white and African-American populations and the Japanese population, with respect to differences in risk factors, as evidenced by anthropometry.

A Postdoctoral Fellow from Ajou University Hospital, Suwon, Korea, received the Glenn Foundation Endocrinology and Aging Award, in June 1998, for research conducted through the Diabetes Section, Laboratory of Clinical Investigation (LCI). (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

A Postdoctoral Fellow from the Russian Academy of Medical Sciences, Moscow, came to the Diabetes Section, LCI. She is studying the signaling events triggered by insulin and its analogues in various experimental models.

The Endocrine Section, LCI, is hosting a Fogarty Fellow from Switzerland. He is a fully trained internist interested in geriatric medicine and gerontologic clinical research. He is assisting with analysis of body composition for the study of intervention with growth hormone and estrogen in women or testosterone in men, which is being conducted by the Endocrine Section. The investigator is also involved in other clinical research studies.

V.
National Institute on Alcohol Abuse and Alcoholism

INTRODUCTION

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is the primary Federal entity responsible for research on the causes, consequences, prevention, and treatment of alcohol-related problems. NIAAA conducts and supports biomedical and behavioral research into the effects of alcohol on the mind and body, prevention and treatment of alcohol abuse and alcoholism, and the epidemiology of alcoholism and alcohol-related problems.

NIAAA's international objectives are carried out through the International Research and Training Program. International activities throughout the offices and divisions of the Institute are coordinated through this Program. Using a variety of initiatives and mechanisms, NIAAA supports the research efforts of scientists worldwide who are investigating questions about alcohol use that are relevant to the U.S. population.

The International Research and Training Program serves as the point of contact for several bilateral agreements with foreign governments and multilateral agreements with international organizations. NIAAA is a designated World Health Organization (WHO) Collaborating Center for Research and Training on Alcohol Problems. The Program consists of international grants, medical education and research training, scientific exchange, and dissemination of information.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

NIAAA is involved in facilitating and participating in international research activities. The Institute sponsors a program announcement, Developmental Grants for Collaborative International Projects. This program teams established U.S. investigators with foreign investigators to develop new research projects on alcohol abuse and alcoholism that are the foundation for more intensive larger studies. Awards have been made for the following research:

- a project with Canadian scientists to study the genetic and neurobiological underpinnings of alcohol-seeking behavior;
- a study with Italian scientists that is examining the neuropharmacological basis of the subjective effects of alcohol;
- a screening program for alcohol-related problems in emergency departments in Mexico; and
- a clinical trial to establish the efficacy of a brief physician intervention for alcohol-use disorders that is delivered in primary care settings in Poland.

Major involvement with binational commissions in Russia and South Africa has facilitated partnerships between U.S. investigators and their counterparts in these two countries.

South Africa

NIAAA's active membership in the Health Working Group of the Gore-Mbeki Binational Commission for South Africa has led to significant progress in research on FAS and in efforts to develop research on prevention and treatment of alcoholism. Studies addressing the problem of FAS are supported jointly by NIAAA and the Office of Research on Minority Health, National Institutes of Health. The South African government recognized that FAS is particularly prevalent in workers on farms and in vineyards of the Western Cape Province and is working with NIAAA on research projects and prevention strategies. The high prevalence of this syndrome in farmworkers derives from a culture of heavy alcohol drinking. This culture developed as a consequence of past practices of providing partial wages to farmworkers in the form of alcohol. A prevalence rate of 5% (50 per 1,000) was documented in the city of Wellington in the western cape, compared with estimates of 0.5–3 per 1,000 in the United States.

A joint team of South African and U.S. researchers are working to ascertain cases of FAS among the first-grade students in 12 schools in Wellington. This is the first comprehensive screening for FAS ever undertaken within a single community. Through this approach, more than 100 cases were identified. The presence of such a large number of cases in a single location supports (a) the conduct of research studies on metabolic and genetic risk factors for vulnerability to FAS and (b) the performance of neurobehavioral studies to characterize the specific nature of cognitive deficits expressed in FAS. To support related studies, the Medical Systems Division, General Electric Corporation, donated a state-of-the-art ultrasound machine to study fetal development in children with prenatal exposure to alcohol. Results of this work were presented at the annual meeting of the Research Society on Alcoholism, in Hilton Head, South Carolina, in June 1998. South African researchers are under the auspices of the University of Witwatersrand. U.S. researchers are from Drew University, Los Angeles, California; Stanford University, California; the University of California, San Diego; the University of Indiana, Indianapolis; Wayne State University, Detroit, Michigan; the University of New Mexico, Albuquerque; State University of New York, Buffalo; Howard University, Washington, D.C.; and the University of Wisconsin, Madison.

A task force worked during fiscal year 1998 to plan strategies for prevention and treatment of FAS. The task force includes administrators, educators, advocates, and community activists from Wellington, as well as an associate professor from Howard University's School of Social Work. Working at the request of the Minister of Health in the eastern cape of South Africa, researchers from the University of Texas, San Antonio, and NIAAA are developing joint research in prevention and treatment of alcohol abuse and alcoholism.

Russia

The NIAAA Director is the lead for alcohol-related problems, on the Gore-Primakov Commission Subcommittee for Joint Activities on Identified Health Issues. Alcoholism is a significant problem in Russia, and work is focusing on three areas: (1) prevention and treatment of alcohol-use disorders in the primary care setting; (2) prevention of alcohol-related problems in adolescents; and (3) prevention and treatment of alcohol-related birth defects.

After 2 years of study, investigators at the University of Minnesota School of Public Health, Minneapolis, and two Russian researchers in prevention, from Moscow, completed evaluation of a school- and community-based intervention for prevention of alcohol problems in preteens in Russia. The intervention was used in fifth graders from 26 public schools in Moscow and their parents. An important finding from baseline measures of 1,300 children was that children in Russia are likely to initiate alcohol use at a very early age: 43% reported alcohol use by the spring of their fifth-grade year. Findings from the outcome measures indicate that parents and children participated in the program at very high rates, comparable to rates seen among U.S. families who participated in a similar program. Children in the intervention program reported having more family rules against drinking of alcohol than control children did, and those in the program did not think their parents would allow them to drink when they were seniors in high school. Furthermore, there was a statistically significant increase in knowledge about alcohol and its effects for children in the intervention group.

Evidence from studies conducted throughout the world shows that primary care physicians can have a substantial effect on the reduction of alcohol use by their patients, before serious problems and addiction occur. Brief intervention delivered by physicians in primary care settings may be beneficial to the heavily stressed Russian health care delivery system, because its implementation does not involve new medications or expensive treatment. This intervention can be accomplished by providing training to practicing clinicians, residents, and medical students. A course for 40 faculty from four medical academies in St. Petersburg focused on the role of primary care physicians in providing screening and brief intervention for misuse of alcohol by patients. The 5-day course was taught by teams of U.S. and Russian faculty from Harvard University Medical School, Boston, Massachusetts; Yale University Medical School, New Haven, Connecticut; the University of Wisconsin, Madison; Pavlov State Medical University, St. Petersburg; and St. Petersburg Post Graduate Academy for Medical Studies. Changes in clinical and teaching practices of the participants will be measured to determine the effectiveness of the course. As a direct result of this activity, a course in alcohol-use disorders was added to the primary care curriculum of Pavlov State Medical University.

In Russia, investigators have started work in improving the diagnosis of fetal alcohol syndrome (FAS) and in shaping and adapting instruments to determine the extent of maternal alcohol use and to conduct neurobehavioral assessments in children. Russian psychologists and physicians have been trained by U.S. experts, and studies of risk factors for maternal misuse of alcohol and prevalence of FAS are under way.

Mexico

Joint research that started 3 years ago among scientists at the Institute of Nutrition, Mexico City, Mexico, Thomas Jefferson University, Philadelphia, Pennsylvania, and Johns Hopkins University, Baltimore, Maryland, has identified a possible mitigating factor for the high rates of death from liver disease in certain districts in Mexico. A traditional alcoholic drink known as pulque, which is made from cactus and is consumed in high quantities in these districts, was identified as a source of endotoxin and live gram-negative pathogenic bacteria, such as *Salmonella* and *Yersinia*. As a result, the Mexican Ministry of Health initiated a commission to investigate the safety and to monitor the production of this beverage.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Australia

Australia's registry of twins allows researchers to study the genetics of alcoholism in a way that it cannot be studied in the United States. Researchers at Washington University, St. Louis, Missouri, are using a data set of twin pairs from Australia to develop and test genetic models for the natural history of alcohol use and abuse across the life span. A combination of computer simulation and theoretical analysis is being used to investigate both multistage genetic models and social and environmental influences on the risk for alcoholism.

Canada

Epidemiologic studies show a high positive correlation between alcohol consumption and tobacco use. Findings from several other studies indicate that alcohol can facilitate the self-administration of nicotine and that, when alcohol and nicotine are taken together, smoking can attenuate the sedating effects of ethanol. Studies of experimental animals suggest potential mechanisms explaining some of these observations in human subjects. Researchers at the University of Indiana School of Medicine, Indianapolis, and the Addiction Research Foundation, Toronto, Ontario, are collaborating on animal studies. Each of the two laboratories has provided a rat strain that exhibits a distinct pattern of alcohol consumption. A Canadian expert on self-administration of nicotine in laboratory animals will assist investigators in addressing the question of alcohol–nicotine interaction.

Human and animal studies have shown that exposure to moderate peak blood levels of ethanol during development results in permanent morphological changes in the cerebellum and cerebrum and in motor and other behavioral deficits. In an animal study funded by NIAAA, researchers at the University of Illinois, Urbana-Champaign, continue to investigate the effects of postnatal alcohol exposure on brain organization and behavioral performance. They are also assessing the potential therapeutic value of intervention programs in patients with alcohol-related neurodevelopmental disorder.

Chile

NIAAA organized and cosponsored the U.S.-Canada-Chile workshop, Genetic Factors in Alcoholism. Cosponsors included the International Center for Alcohol Policies; the faculties of Medicine and Chemical and Pharmaceutical Sciences, University of Chile, Santiago; Ahumada Pharmacies, Santiago;

and Consejo Nacional de Ciencia y Technologia. The workshop was held in Santiago, on January 4–6, 1999, in honor of Professor Jorge Mardones, who is deceased. It was Professor Mardones, of the University of Chile, who in the 1940's, first proposed that the appetite for alcohol is genetically controlled. To test this important assumption, he selectively bred mice to produce a strain with high rates of alcohol consumption. He then crossbred "nondrinking" rats to generate a strain that rejected alcohol. These studies, which were confirmed in Canada, Finland, Italy, and the United States, contributed to the expansion of research into the genetics of alcoholism. Professor Mardones remained active in teaching, mentoring, and research until his death, at the age of 90 years, in December 1998. Scientific experts from Canada, Chile, and the United States who have developed this area of science met in Santiago to review recent clinical and experimental advances and to plan collaborative efforts among scientists in these countries.

India

Researchers at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Washington University, St. Louis, Missouri, and NIAAA completed a study on neurophysiological correlates of recovery from alcoholism. The project, which began in 1993, focused on measures of neurocognitive function in persons with chronic alcoholism. Investigators evaluated neurocognitive function after detoxification at the NIMHANS inpatient treatment facility and in follow-up visits at 3 months, 6 months, 1 year, and 2 years after detoxification. They assessed function by using standardized diagnostic, personality, and neuropsychological instruments, as well as electroencephalography to measure attention, motor control, and perceptual judgment. Findings demonstrate a number of specific deficits of attention and information processing in persons with alcoholism. These deficits were greatest and most resistant to recovery in those with a strong familial history of alcoholism.

Ireland

Genetic factors clearly are an important contributor to alcohol dependence. Current evidence suggests that the probability of detecting susceptibility genes of complex traits such as alcohol dependence can be enhanced by such methods as the use of large samples that have been selected and systematically ascertained from a population with substantial genetic and cultural homogeneity. The Health Research Board, Dublin, Ireland, and experts at the Medical College of Virginia, Richmond, are collaborating on a study in three counties in Ireland. The study is a genetic assessment of 1,700 siblings from 800 multiplex sibships who meet the criteria for alcohol dependence of the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition.

Italy

Researchers at Bowman Gray University School of Medicine, Winston-Salem, North Carolina, and the University of Calgari, Sardinia, are working to characterize the neuropharmacological basis of the subjective effects of alcohol in rats that were bred to prefer to drink intoxicating quantities of alcohol. Rats that either prefer to drink ethanol (sP) or that do not prefer to drink ethanol (sNP) were selectively bred in Italy. This breeding also produced rats that greatly differ in their innate degree of "anxiety." The sP rats display more behaviors indicating anxiety than the sNP rats do. This finding suggests that an anxiogenic phenotype may be linked to high preference for and consumption of ethanol. In support of such a causal relationship, the voluntary ethanol intake of sP rats significantly reversed their anxiogenic state. These data indicate that the action of ethanol at γ-aminobutyric acid and 5-hydroxytryptamine receptors, which are known to mediate subjective feelings of anxiety, may contribute to the promotion and maintenance of high ethanol intake.

Japan

Japan is the only developing country that continues to show an increase in per capita alcohol consumption. On November 10–12, 1998, a joint symposium entitled Cross-cultural Issues in Alcohol Research: U.S.-Japan Research Development Workshop took place in Tokyo. The meeting was jointly sponsored by NIAAA, the National Institute on Alcoholism, Kuryama National Hospital, and the Japanese Ministry of Health and Welfare. Researchers from throughout Japan met with senior U.S. investigators in the areas of liver disease, genetics, neuroscience, pharmacotherapy, and epidemiology, to determine priorities for joint research projects. An important secondary agenda of the meeting was to provide support for young Japanese researchers just entering the field of alcohol research and to facilitate their work. Posters from new investigators were featured on each day of the meeting, and the authors were able to benefit from feedback provided by the senior investigators from the United States. Japanese presenters were from Kyoto Prefectural Medical University, Kawaski Medical University, Yokohama Maioka Hospital, the University of Tsukuba, Kanazawa Medical University, Sapporo Medical University, Tokyo Medical and Dental University, Ichikawa General Hospital, and Kyorin University School of Medicine. U.S. research programs include the University of Connecticut Health Sciences Center, Farmington; the University of Miami School of Medicine, Florida; the University of Indiana School of Medicine, Indianapolis; the State University of New York Medical Center, Brooklyn; the University of North Carolina School of Medicine, Chapel Hill; Wake Forest University School of Medicine, Winston-Salem, North Carolina; and the University of Texas School of Public Health, Dallas. A supplement to the alcohol research journal, *Alcoholism: Clinical and Experimental Research,* will feature summaries of the research reports presented at the workshop and abstracts of meritorious posters from the young Japanese investigators.

Mexico

The prevalence of alcohol-use disorders among patients seen in hospital emergency departments is high. This finding suggests the need for screening programs to detect misuse of alcohol, but current instruments do not perform well across genders and ethnic subgroups. Investigators at the Alcohol Research Group, Berkeley, California, and the Institute of Psychiatry, Mexico City, completed a study to determine optimal screening items for identifying persons who may benefit from a brief intervention in the emergency department setting, for problem drinking of alcohol. Study participants were patients seen in the emergency department in hospitals in Mexico and the United States. A core set of items from a series of standard assessment instruments were identified as optimal for use in a screening program for both genders and including various ethnic groups.

Individual differences in the propensity to develop alcoholic liver disease suggest that codependent variables are likely to influence susceptibility to alcohol-induced hepatotoxicity. Researchers at Johns Hopkins University, Baltimore, Maryland, and Instituto Nacional del Nutricion, Mexico City, are studying a group of Mexican patients with alcoholism who are likely to have enteric infections. The scientists hypothesize that infection with gram-negative enteric pathogens potentiates the genesis of alcoholic liver disease by increasing hepatic cytokine production. In addition, scientists at the institute examined the beverage pulque, a Mexican beer that is consumed in regions with a high prevalence of alcoholic liver disease. They determined that it is a source for enteroinvasive bacteria and endotoxin. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

Poland

Investigators at the University of Wisconsin, Madison, and the Polish Institute of Psychiatry and Neurology are collaborating on a large clinical trial to test the efficacy of brief intervention by physicians in primary care clinics throughout Poland. Twenty family physicians from 12 community practice sites in Poland are participating in the study, and more than 3,000 patients have been screened for alcohol-use disorders.

Russia

NIAAA, the University of North Dakota Medical School, Grand Forks, and the Department of Obstetrics, Pavlov State Medical University, St. Petersburg, are conducting a study to determine the risk factors for misuse of alcohol by Russian women of childbearing age. Information from this research will be used to develop prevention strategies. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

Spain

Researchers at the University of California, Los Angeles, School of Medicine and the University of Barcelona are collaborating on a study to elucidate the mechanism and importance of ethanol-induced deficit in the uptake of glutathione (GSH) by hepatic mitrochrondia. This condition impairs the body's defense against oxidative stress. Study results suggest that ethanol-induced impairment of transport of GSH into mitochondria is selective and that it is mediated by decreased fluidity of the mitochondrial membrane, which is prevented by treatment with *S*-adenosylmethionine.

Activities With International and Multinational Organizations

International Council on Alcohol and Addictions

The 42nd International Council on Alcohol and Addictions International Institute on the Prevention and Treatment of Dependencies was held in St. Julian's, Malta, on August 30–September 4, 1998. NIAAA sponsored a 1-day science symposium, Alcohol Research: From Basic Science to Public Policy. The meeting included NIAAA-funded researchers in the areas of alcohol research and public policy; moderate drinking; effects of alcohol on the brain and nervous system; alcohol-induced liver damage; epidemiology and prevention of FAS; the psychosocial basis of alcohol-related problems; the biological basis of alcohol-related problems; new directions in treatment of alcoholism; and effective prevention interventions for young persons. In addition, the NIAAA Director gave a keynote presentation at the Congress on Alcohol Prevention and Treatment Strategies.

International Society for Biomedical Research on Alcoholism

NIAAA provided support for the biennial meeting of the International Society for Biomedical Research on Alcoholism, which was held in Copenhagen, Denmark, in July 1998.

World Health Organization

NIAAA has been a WHO Collaborating Center for Research and Training on Alcohol Problems since 1987. Active collaborations exist with WHO Headquarters, Geneva, Switzerland; the Pan American Health Organization, Washington, D.C.; and the WHO European Regional Office, Copenhagen, Denmark. NIAAA continues to have a significant role in the WHO-NIH joint project on diagnosis and classification of mental disorders and alcohol-use and drug-use disorders.

NIAAA provides funding for a major project that is led by the University of California, San Francisco, in collaboration with WHO and a number of centers in foreign countries. The Collaborative Alcohol-Related Longitudinal Project involves more than 20 longitudinal data sets that are analyzed through meta-analysis and other multivariate techniques to examine long-term risk factors, drinking patterns, and consequences of alcohol use. Recent analyses of three general population surveys of adult women found that odds of death for former drinkers and for persons who practiced long-term abstention from alcohol were greater than those for light drinkers. However, odds of death for moderate and heavy drinkers were greater than those for light drinkers. These results were consistent with the hypothesis that characteristics of abstainers other than their nonuse of alcohol may account for their higher mortality risk. On the other hand, in an analysis of eight surveys of men in the general population, no evidence was found for the hypothesis that abstinence is associated with greater mortality risk than light drinking. The most consistent finding across studies was the association of heavy drinking with mortality among young persons.

Intramural Programs and Activities

During fiscal year 1998, 19 scientists representing 11 countries conducted research in NIAAA's intramural laboratories. In addition, NIAAA intramural scientists were involved in several joint projects with researchers in foreign laboratories.

Laboratory of Clinical Studies

The Laboratory of Clinical Studies is conducting two important research projects in conjunction with University College, London, England, and the University of Haifa, Israel. These projects have two aims: (1) to uncover, assess, and contrast mechanisms responsible for impairments in cognitive functioning in different forms of neuropsychiatric disorders, especially in syndromes associated with alcohol abuse, and (2) to increase understanding of how drugs alter cognitive functioning and memory in persons with alcoholism.

Laboratory of Membrane Biochemistry and Biophysics

In the Laboratory of Membrane Biochemistry and Biophysics, four studies are being conducted with foreign institutions. Researchers at the Institute of Nutrition and Food Technology, University of Chile, Santiago, are collaborating on a study entitled Desaturation of Essential Fatty Acids Using Stable Isotope GC-MS (gas chromatography-mass spectroscopy). This project is a metabolic study of persons with alcoholism. The findings suggest previously unknown mechanisms for the effects of alcoholism on concentrations of fatty acids in tissues.

Working with scientists at Oxford University, England, and Tottori University, Japan, NIAAA intramural scientists are trying to understand the metabolic disorders resulting from decreases in activity of the pyruvate dehydrogenase (PDH) multienzyme complex. PDH activity is key to providing substrates for the Krebs tricarboxylic acid cycle, and decreased PDH activity decreases the major intermediates necessary for production of cellular energy. During the consumption of alcohol, PDH in the liver is completely inhibited, and investigations are under way to determine the effects of the metabolic product of alcohol (acetate) on brain PDH activity and neuronal function. These studies have led to the possibilities for treatment of common diseases other than alcoholism, such as parkinsonism and Alzheimer's disease. After recent review by the Institute of Medicine, these studies also have led to collaborative research with the U.S. Department of Defense for improved methods of treating severe trauma and burns.

Finally, Laboratory staff are collaborating with the University of Leipzig, Germany, in investigation of (a) the interaction of alcohol with proteins and lipids in biological membranes; (b) the structure and dynamics of membranes composed of lipids with polyunsaturated fatty acids; and (c) lipid–protein interactions related to alcoholism and polysaturation of lipids.

Laboratory of Molecular and Cellular Neurobiology

The Laboratory of Molecular and Cellular Neurobiology, Aalborg, the University of Aalborg, Denmark, the University of Helsinki, Finland, the Max Planck Institute, Germany, and the Human Frontiers Science Program, Japan, conducted an investigation of the molecular structure–function relationships of neurotransmitter receptors and the molecular mechanisms of action of alcohol and neuroactive substances on those receptors.

Laboratory of Neurogenetics

Intramural researchers in the Laboratory of Neurogenetics are collaborating with scientists at the University of Helsinki, Finland, on human and animal studies of deficits in serotonin function that can shed light on the role of serotonin in behavior. They are also looking at the role of milder functional variants in serotonin genes in the predisposition of persons to psychopathologies including alcoholism.

Laboratory staff are working with investigators from the Karolinska Hospital, Stockholm, Sweden, to identify persons with deficits in metabolism of serotonin in the central nervous system. It is hypothesized that this deficit is related to poor control of impulses in persons with alcoholism.

A group of scientists from McGill University, Montreal, Quebec, the University of Helsinki, Finland, and the University of Pisa, Italy, are working with NIAAA investigators to screen the TD02 gene for polymorphisms, assess functionality, and search for disease associations. This research is based on the hypotheses that genetic defects in the enzymes involved in serotonin metabolism contribute to several neuropsychiatric diseases, including alcoholism, eating disorders, obsessive–compulsive disorder, and autism.

Scientists from Seoul National University, Korea, and the Taipei Blood Center, Taiwan, are working with scientists at NIAAA to examine sequence variation within the nonpseudoautosomal region of the Y chromosome in the Hominidae family. This study should add to knowledge about evolution of the Y chromosome and paternal history in the human population.

Laboratory personnel are also working with Netherlands Institute for Public Health, Leiden, on a study of the effects of alcohol intake on genomic DNA.

VI.

National Institute of Allergy and Infectious Diseases

INTRODUCTION

The National Institute of Allergy and Infectious Diseases (NIAID) can trace its origin back to the Laboratory of Hygiene established on Staten Island, New York, in 1887. The Laboratory of Hygiene evolved into the National Microbiological Institute, which was renamed the National Institute of Allergy and Infectious Diseases in 1955, in recognition of the importance of the immune system to human health and disease. When the Office of International Research of the National Institutes of Health (NIH) disbanded in 1968, NIAID assumed responsibility for the Office's International Centers for Medical Research and Training Program. NIAID subsequently assumed lead NIH responsibility for research on influenza (1974), sexually transmitted diseases (STDs) (1974), and human immunodeficiency virus (HIV) (1986).

NIAID is organized into five divisions. The Division of Intramural Research is responsible for coordinating the research conducted in NIAID laboratories. Three extramural divisions fund research outside the NIH: the Division of Microbiology and Infectious Diseases (DMID); the Division of Allergy, Immunology, and Transplantation; and the Division of AIDS (acquired immunodeficiency syndrome) (DAIDS). The Division of Extramural Activities is responsible for initial review groups convened by NIAID, administrative management of external awards, and secretariat support to the National Advisory Allergy and Infectious Diseases Council.

NIAID is the third largest component of the NIH, which is the research arm of the U.S. Public Health Service (PHS), a domestic agency. Authority for the NIH to conduct international research was formally defined in the PHS Act of 1963, which limited studies to "international research relevant to the health and welfare of U.S. populations." The PHS Act of 1988 ("AIDS" Act) expanded this authority to training, technology, and institutional strengthening for research in HIV/AIDS and related areas but provided no additional funding for these international activities. In fiscal year 1994 (FY 94), NIAID was, for the first time, given a specific mandate for tropical disease research. NIAID uses six mechanisms to conduct international research: (1) collaborative research with the Division of Intramural Research; (2) awards for foreign research; (3) awards for domestic research with foreign components; (4) bilateral programs; (5) interagency agreements; and (6) multilateral activities.

Division of Intramural Research

The Division of Intramural Research is organized into 16 laboratories: the Laboratory of Allergic Diseases; Laboratory of Cellular and Molecular Immunology; Laboratory of Clinical Investigation; Laboratory of Host Defenses; Laboratory of Immunogenetics; Laboratory of Immunology; Laboratory of Immunopathology; Laboratory of Immunoregulation; Laboratory of Intracellular Parasites; Laboratory of Infectious Diseases; Laboratory of Microbial Structure and Function; Laboratory of Molecular Microbiology; Laboratory of Molecular Structure; Laboratory of Parasitic Diseases; Laboratory of Persistent Viral Diseases; and Laboratory of Viral Diseases. The laboratories are concentrated on the NIH campus in Bethesda, Maryland, but some are also located in Rockville and Frederick, Maryland, and at the Rocky Mountain facilities in Hamilton, Montana.

In the Division of Intramural Research, there are 89 tenured scientists; 4 tenured clinicians; 21 tenure-track scientists; 513 nontenured scientists (one-third from foreign countries); and 406 nonscientist support staff. During FY 97, foreign scientists from 43 countries and Taiwan received time-limited research training at NIAID. The largest national groups were from Italy (22), Japan (21), France (19), Canada (13), China (11), Germany (10), Russia (9), Spain (8), the United Kingdom (8), India (6), and Korea (6). Other countries represented were Algeria, Argentina, Australia, Austria, Bangladesh, Belgium, Bolivia, Brazil, Colombia, Croatia, the Czech Republic, Denmark, Greece, Hungary, Iceland, Iran, Israel, Jordan, Mali, Mexico, Morocco, the Netherlands, New Zealand, the Philippines, Poland, Portugal, Slovakia, Swaziland, Switzerland, Thailand, Turkey, and Uzbekistan. The personnel in this Division constitute the majority of NIAID staff but only about 10% of the NIAID budget.

Extramural Research

NIAID support for extramural research is the primary source of funding for civilian investigators in U.S. universities and research institutions in the areas of HIV/AIDS, STDs, tropical diseases, tuberculosis, and the development and evaluation of human vaccines. Extramural research accounts for about 90% of the NIAID funding but only about 10% of staff positions. Historically, DMID has been responsible for most NIAID collaborative research on endemic disease problems of tropical or developing countries. For the past decade, however, DAIDS has funded major international studies in resource-poor settings overseas.

In contrast to many domestic research agencies, NIAID allows foreign investigators to apply directly for investigator-initiated research grants and, under certain circumstances, to respond to solicited Program Announcements, Requests for Applications, and Requests for Proposals. The rivalry for investigator-initiated grants and other awards, however, is so competitive that direct application is not practical for most overseas scientists. A more effective strategy for foreign scientists is to identify a U.S. collaborator with experience and success in writing applications for NIH grants. Collaborative proposals can then be submitted to the NIH by the U.S. partner. If peer review finds the proposal to be competitive, NIAID provides funds to the U.S. institution to carry out both the domestic and foreign components of the proposal. In research areas such as international tropical diseases, vaccine evaluation, and AIDS, proposals for research in resource-poor settings often do not compete successfully in the general pool of grants. To fulfill its research mission, NIAID develops special funding mechanisms, reserves funds, and solicits applications that compete against each other for the set-aside funds.

DMID supports four special international programs:

1. Tropical Disease Research Unit (TDRU) awards support multidisciplinary centers of research excellence in the United States.
2. The International Collaboration in Infectious Disease Research (ICIDR) Program provides funding to U.S. institutions to link up with foreign institutions in developing countries.
3. Tropical Medicine Research Center (TMRC) awards are direct funding to outstanding institutions in the tropics.
4. The Tuberculosis Prevention Research Center supports a U.S. university to coordinate a network of domestic and international centers for research on this reemerging disease.

In 1997, NIAID initiated three new Emerging Viral Diseases Research Centers and four Viral Hepatitis Research Centers as part of the Emerging and Reemerging Infectious Diseases Research Initiative.

To more closely coordinate and monitor international research activities, NIAID established the International Centers for Tropical Disease Research Network in 1992. This network consists of

1. the NIAID Office of Tropical Medicine and International Research;
2. the NIAID Laboratory of Parasitic Diseases, Laboratory of Malaria Research, and other intramural laboratories;
3. institutions that are TDRU, ICIDR, and TMRC participants; and
4. other U.S. institutions receiving substantial NIAID support for research in tropical medicine.

The International Centers for Tropical Disease Research Network convenes each spring in an open scientific meeting in Bethesda, Maryland, for coordination, exchange, and identification of research needs and opportunities.

In 1987, DAIDS launched the International Collaboration in AIDS Research (ICAR) Program, modeled after the ICIDR Program. The ICAR awards were succeeded by the more focused Preparing for AIDS/HIV Vaccine Evaluation (PAVE) linkage awards, which supported U.S. institutions for an intensive 2-year effort to work with colleagues in developing countries in training, technology transfer, and strengthening of institutions. DAIDS now supports an international AIDS Vaccine Master Contract, through which awards are made to U.S. institutions and two South African institutions to participate in the HIV Network (HIVNET). These institutions conduct specific HIV/AIDS prevention or intervention projects in the United States or developing countries.

Bilateral Activities

NIAID's country-to-country activities run the gamut from direct scientist-to-scientist collaboration to formal agreements at NIAID, the NIH, PHS, and the presidential level. NIAID participates in bilateral agreements with 17 countries and Taiwan. The countries are Brazil, China, Croatia, Finland, France, Georgia, Germany, India, Israel, Italy, Japan, Macedonia, Mongolia, Poland, Russia, Slovenia, and South Africa. For some of these agreements, extrabudgetary funds are available from the U.S. Agency for International Development (USAID), the U.S. Department of State, or the Special Foreign Currency (Public Law 480) Program, but most are implemented with regular NIAID resources.

Interagency Agreements

In the current period of expanding scientific opportunity and finite resources in U.S. Government agencies, it is increasingly common for agencies to combine resources to carry out joint programs. During FY 98, NIAID managed three interagency agreements with USAID and one with the National Aeronautics and Space Administration (NASA).

Multilateral Activities

Infectious diseases, including AIDS, are the major causes of preventable death and disease throughout the world, and new knowledge and advances made possible by NIAID research are important for the global prevention, treatment, and control of these conditions. The World Health Organization (WHO) is the lead United Nations agency in health. In FY 97, NIAID initiated a $1.0 million contribution for research on malaria to the Special Program for Research and Training in Tropical Diseases of the WHO/World Bank/United Nations Development Program. In addition, NIAID scientists and awardees participate extensively in WHO advisory committees and steering committees on AIDS, infectious diseases, tropical diseases, and immunology. Some NIAID laboratories and programs also serve as WHO Collaborating Centers in Antiviral Agents (DMID) and in Epidemiology of Asthma and Allergic Diseases (Division of Allergy, Immunology, and Transplantation); Collaborating Centers in Microbial Vector Research (Laboratory of Viral Diseases); and AIDS Reagent Centers (DAIDS).

NIAID has a close working relationship with the Regional Office of WHO for the Americas and with the Pan American Sanitary Bureau, which is the health component of the Organization of American States. NIAID is also a member of the consortium of United Nations agencies (e.g., WHO and the United Nations International Children's Emergency Fund) and other organizations participating in the Childhood Vaccine Initiative. The role of NIAID's DMID is to invest in basic and applied research leading to the development and evaluation of new or improved pediatric vaccines.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

AIDS

Scientists in the Laboratory of Immunoregulation (NIAID) documented that, shortly after infection with HIV, the virus enters resting (nondividing) CD4+ T cells. The pool of cells of the immune system with latent infection is established even if, soon after acute infection, a patient is treated with powerful antiretroviral drugs that reduce plasma levels of virus to extremely low or undetectable levels.

Within the domestic Multicenter AIDS Cohort Study, Federal University, Bahia, Brazil, participated in a nested case–control study of interleukin 6 (IL-6) and AIDS-associated Kaposi's sarcoma. Variables of sexual behavior did not confound the association between IL-6 and Kaposi's sarcoma. Higher-than-expected IL-6 levels among control subjects could be explained by the association of higher IL-6 levels with lower CD4+ T-cell counts. Thus high levels of IL-6 may be a sign of immune dysfunction among HIV-positive persons.

A large 2-year study supported by NIAID in Cameroon demonstrated that a vaginal contraceptive film containing a commonly used spermicide (nonoxynol 9) reduced STDs but had no effect on transmission of HIV/AIDS.

Investigators at the Aaron Diamond Research Center, New York City, New York, and Oxford University and the Institute of Molecular Medicine, Oxford, England, found a direct relationship between the activity of cytotoxic T lymphocytes and the plasma load of human immunodeficiency virus type 1 (HIV-1).

The Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, coordinated a study involving Finland, Kenya, and Trinidad and Tobago, to determine the risks of disseminated bacille Calmette-Guérin (BCG) or *Mycobacterium tuberculosis* in adults with AIDS. The study found that the risk of disseminated BCG among adults with AIDS who were vaccinated as children was very low. Childhood BCG vaccination was also associated with protection against bacteremia due to *M. tuberculosis* among adults with advanced AIDS.

During FY 98, the University of Washington HIVNET studied urethral infections in transport workers in Mombasa, Kenya, and found a prevalence of 3.4% for *Neisseria gonorrhoeae,* 3.4% for *Chlamydia trachomatis,* and 6.0% for *Trichomonas vaginalis*. Of those infected, almost two-thirds were asymptomatic. Complaints of a discharge were more predictive of infection than clinical examination. A positive leukocyte esterase dipstick test predicted infection with a sensitivity of 95% and a specificity of 59.3% in men with symptoms, but only 55.3% and 82.8%, respectively, in men with no symptoms. The researchers recommend that, in resource-poor settings with high prevalence of urethral infection, an effective screening and management strategy would be to treat all men with symptoms, as well as men with a positive leukocyte esterase dipstick test, for all three infections.

The Johns Hopkins HIVNET supports collaboration between Johns Hopkins University, Baltimore, Maryland, and the Malawi College of Medicine, Blantyre, to carry out clinical trials of HIV/AIDS prevention. With the National Cancer Institute (NCI), NIH, the HIVNET performed a prospective evaluation of the risk factors for HIV-1 positivity of cord blood among HIV-positive infants. Contrary to expectations, positivity of cord blood for HIV-1 did not identify a subset of infants infected in utero. These results suggest that the timing and routes of HIV transmission are similar for HIV-positive infants and for those with positive or negative cord blood. Lactoferrin, an iron-binding glycoprotein, is a component of nonspecific immunity to a variety of microbes. In the HIVNET population, low maternal levels of circulating lactoferrin appear to be associated with increased HIV transmission from mother to infant.

At the University of California, Los Angeles, investigators working with female commercial sex workers at four sites in the southern Philippines over a 3-year period compared the effect of peer education, self-sufficiency, and skills for negotiating condom use (site 1); manager or supervisor support (site 2); a combination of the elements of sites 1 and 2; and conditions at a control site. The control site had a slight increase in STD rates and four HIV-1 seroconversions, compared with STD reduction and no HIV-1 seroconversions at the intervention sites. A multivariate structural equation model identified significant predictors of condom use and efficacy. The lessons learned are being integrated into the participating Social Hygiene Clinics and brothels. An expanded approach for education of commercial sex workers in high-risk Philippine communities is being developed.

The Ivanovsky Institute of Virology, Moscow, Russia, participated with Johns Hopkins School of Hygiene, Baltimore, in studies showing that North American strains of HIV-1 found in intravenous drug users were also present in intravenous drug users in Northern Europe. Johns Hopkins School of Hygiene, the Research Institute of Pure Biochemicals, St. Petersburg, and the Ivanovsky Institute of Virology, with NCI (NIH), carried out a molecular epidemiology study of HIV-1 in St. Petersburg. The study showed that the homosexual population was infected primarily with North American type B clades and that the heterosexual population had reactivity to A, B, C, D, and E clades, with African types predominant. The African types were introduced earlier, but the B clade has spread more rapidly.

The Albert Einstein College of Medicine, Bronx, New York, and the Swiss Serum and Vaccine Institute, Basel, found that a V3 loop synthetic HIV-1 peptide conjugated to purified protein derivative was safe and immunogenic when administered to HIV-negative volunteers. This HIV vaccine prototype can be rapidly and inexpensively modified to include other peptide epitopes and is especially suitable for use in populations primed by BCG vaccination, populations at high risk of exposure to *M. tuberculosis,* or those with both characteristics.

Canton Hospital, St. Gallen, Switzerland, is collaborating with the University of North Carolina, Chapel Hill, John Snow, Inc. (United States), and Princess Elizabeth Hospital, Blantyre, in studies of CD4+ T-cell levels in blood, of HIV-1 RNA concentrations in seminal plasma, and of genital ulcer disease in men in Malawi. To date, the investigators have determined that factors associated with HIV shedding in semen depend on variables such as stage of disease, antiretroviral therapy, and concomitant systemic or mucosal infections, including STDs. In studies in Switzerland and the United States, they confirmed a strong correlation between seminal cell culture and concentrations of HIV RNA in seminal plasma. The findings suggest that HIV is released from productively infected cells in the male genital tract. This hypothesis was strengthened by the observation of reduced concentration of HIV in the semen after treatment with antiretroviral drugs. With colleagues at the University of Zürich, Switzerland, the investigators determined that reductions of HIV RNA after treatment are more dramatic in blood than in semen. The research group is investigating levels of HIV-1 in the semen during primary infection and their importance in transmission to sexual partners.

The Johns Hopkins HIVNET supports collaborative research with Chiang Mai University, the Royal Thai Ministry of Health, and the Royal Thai Army Medical Corps. Self-treatment for STDs is common in Thailand, but its effect on HIV risk has not been studied. A cross-sectional report from a cohort of military conscripts revealed that the majority of men with any STD (65.2%)

treated themselves with antibiotics and that 8.5% used antibiotics before sexual activity with commercial sex workers. Among those who frequently engaged in such activity, almost all (98.7%) took preventive steps after sexual activity by increasing urine output (69.2%), washing the genital area (28.9%), or taking antibiotics (0.9%). Men reporting self-treatment for STD were less likely to be infected with HIV (odds ratio, 0.53; 95% confidence interval, 0.31–0.93).

The HIVNET has shown a remarkable increase in use of multiple condoms and a reduction in condom breakage or slippage, in Thailand in 1992–1996. Breakage with use of a single condom declined from 5.9% to 1.6% of sexual acts; use of two condoms increased from 2.8% to 49%; and breakage with use of two condoms was only 0.2%. The decline in breakage or slippage was attributable to greater expertise in condom use by commercial sex workers and clients, in response to the successful national "100% Condom Use Campaign."

The Case Western Reserve HIVNET is planning a phase I study of a live vector HIV vaccine followed by a recombinant subunit vaccine, in Uganda, in FY 98.

Bacterial Diseases

The University of Virginia ICIDR is developing and evaluating new approaches to treating chronic diarrhea in high-risk populations. With the University of Maryland School of Medicine, Baltimore, the ICIDR reported that enteroaggregative *Escherichia coli* produce intestinal inflammation and growth impairment and induce IL-8 release from intestinal epithelial cells. ICIDR scientists observed that glutamine, the major metabolic substrate for enterocytes, drives sodium transport in the gut as well as or better than glucose. The ICIDR, therefore, is conducting clinical trials of oral rehydration solutions containing glucose or glutamine in HIV-positive patients with prolonged diarrhea at Hospital São José, Fortaleza, Brazil. The scientists found that recovery from disruption of the intestinal barrier was more rapid in patients receiving glutamine-based solution than in those receiving standard glucose solution, as determined by ratios of lactulose to mannitol excreted.

Harvard Medical School, New England Medical Center, and Tufts University School of Medicine, Boston, Massachusetts, and Valaisans Hospital, Sion, Switzerland, identified metalloproteinases in the cerebrospinal fluid of patients with Lyme disease that may be a useful marker to diagnose neuroborreliosis.

Emerging Infectious Diseases

Yale University School of Medicine, New Haven, Connecticut, performed a study in Brazil, Colombia, Mexico, and Venezuela on the origins of dengue virus type 2, which is highly pathogenic. Comparative work with viral strains from Bangkok, Thailand, suggests that virulent genotypes in the Americas originated in southwest Asia and have displaced the Native American genotypes.

Scripps Research Institute, La Jolla, California, the University of California, Los Angeles, School of Medicine, St. Jude Children's Research Hospital and the University of Tennessee, Memphis, Federal University, Rio de Janeiro, Brazil, the University of Kiel, Germany, Istituto Superiore di Sanità, Rome, Italy, and Hokkaido University, Japan, have identified, in the tracheae of pigs, cell-surface receptors for both human and avian influenza A viruses with epidemic potential. The researchers are investigating the molecular basis of this finding.

The State University of New York, Stony Brook, and the Carlos III Institute of Health, Madrid, and Hospital General Basico, Málaga, Spain, isolated a new *Borrelia* spp. from patients with relapsing fever, in southern Spain. The organism is closely related to other tick-borne agents of relapsing fever in Africa and Europe, but it causes a relapsing systemic disease with serological similarities to Lyme borreliosis.

Genetic Factors

NIAID is funding the University of Minnesota, Minneapolis, and Bowman Gray School of Medicine, Winston-Salem, North Carolina, to participate in a multicenter, international study of the linkage of human leukocyte antigen (HLA) genes to mite-sensitive asthma. Preliminary results suggest that genetic susceptibility to asthma and mite-sensitive asthma may be mediated partly by genes in the HLA complex on chromosome 6p21.3. Participating institutions include the University of Cartagena, Colombia; Oxford University, England; Institut Pasteur, Paris, France; the National Research Council, Rome, Italy; the Institute of Immunology, Lisbon, Portugal; and the University of Madrid, Spain.

Immunology

NIAID sponsored an international study to evaluate the CDC (Centers for Disease Control and Prevention)-Arthritis Foundation bank of reference sera for antinuclear antibodies, in Atlanta, Georgia, in relation to its usefulness for diagnosis of autoimmune disorders. Participating institutions were the Flinders Medical Center, Bedford Park, Australia; the University of Vienna, Austria; the University of Calgary, Alberta; the Kennedy Institute of Immunology, London, England; the University of Erlangen, Germany; Juntendo University School of Medicine, Tokyo, Japan; and the University of Nijmegen, the Netherlands.

Parasitic Diseases

NIAID sponsors the International *Mycobacterium avium* Complex Study Group, which includes the Veterans Affairs Medical Center, Boston, Massachusetts; the Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; Virginia Polytechnic Institute, Blacksburg; Aurora Hospital, the Ministry of Health, and Tempere University Hospital, Helsinki, Finland; Kenyan Medical Research Institute, Nairobi; and the University of the West Indies, Port of Spain, Trinidad and Tobago. The study group found that rates of disseminated *Mycobacterium avium-intracellulare* were higher in HIV-positive patients in developed countries than in developing countries, because of differences in exposure and immunity. Risk factors for *M. avium-intracellulare* included a low CD4+ T-cell count, swimming in an indoor pool, history of bronchoscopy, regular consumption of raw or partially cooked fish or shellfish, and treatment with granulocyte colony-stimulating factor.

Scientists in the Laboratory of Parasitic Diseases (NIAID) reported in FY 98 that IL-12 in combination with antibiotics is effective in controlling *M. avium* in mice. (IL-12 is a cytokine that regulates cell-mediated immunity through the induction of interferon γ [IFN-γ].) Staff from the Warren Grant Magnuson Clinical Center and NIAID are enrolling HIV-1–positive patients who have disease secondary to *M. avium-intracellulare* in a phase I study of combination therapy with IL-12 and standard antibiotic regimens used against *M. avium-intracellulare.*

The University of Illinois, Rockford, and the Tokyo Medical College, Japan, evaluated the effectiveness of *N,N*-diethyl-*m*-toluamide (Deet) on the penetration and migration behavior of cercariae of *Schistosoma mansoni,* both in vitro and in vivo in the mouse model. Deet was 100% effective in vitro in killing cercariae and 99% effective in vivo in preventing cercariae from penetrating the intact skin in concentrations used in commercial insect repellents. Radiolabeling studies did not demonstrate migration of cercariae to the lungs.

Johns Hopkins School of Hygiene, Baltimore, Maryland, and the Institute for Medical Research, Goroka, Papua New Guinea, conducted a double-blind, placebo-controlled, prospective trial, which showed that zinc supplementation can reduce malaria-related morbidity in preschool children.

In Peru, the John Hopkins ICIDR field tested a new enzyme-linked immunosorbent assay (ELISA) for specific antigen, to detect viable metacestodes in the brains of patients with neurocysticercosis. The assay was performed before and after drug or surgical therapy. A major objective of the ICIDR is to evaluate the effectiveness of a controlled field intervention program for cysticercosis. *Taenia solium* larvae and adults were treated with oxfendazole in pigs and with praziquantel or albendazole in humans. Time–response curves suggest that mass treatment of pigs with oxfendazole may be a simple, effective, inexpensive, and potentially sustainable method of decreasing the porcine reservoir of cysticercosis in countries where the disease is endemic.

Sexually Transmitted Diseases

Infection with *Chlamydia trachomatis* in the United States is primarily an STD, but in water-deprived tropical regions, it remains the leading cause of preventable blindness. Observations in STD clinics that a single dose of the antibiotic azithromycin cured patients infected with *Neisseria gonorrhoeae* and *C. trachomatis* has led to use of the agent for symptomatic treatment of STDs in the tropics, to reduce the burden of STDs, which increase the risk of HIV infection. A single dose of azithromycin has also been effective in curing patients with nonvenereal *C. trachomatis* infection of the eye. In efforts to avert the danger of reinfection, NIAID-supported investigators from the University of California, San Francisco, Johns Hopkins School of Medicine, Baltimore, Maryland, and the London School of Hygiene and Tropical Medicine, England, conducted community-wide treatment programs with azithromycin at sites in Egypt, the Gambia, and Tanzania. This treatment eliminated the disease. Current efforts involve assessing the feasibility and effectiveness of yearly treatment to sustain elimination of trachoma; evaluating the role of nasal carriage in persistence of the disease or reinfection; and using gene typing to carry out molecular epidemiology studies of the introduction and spread of new chlamydial strains.

Tropical Medicine

Investigators at the University of South Florida, Tampa, Harvard Medical School, Boston, and NemaPharm, Cambridge, Massachusetts, Baylor College of Medicine, Houston, Texas, the University of Ghent, Belgium, and the University of Edinburgh, Scotland, have developed an evolutionary framework for the phylum *Nematoda.* They have identified five major clades within the phylum and suggest that animal parasitism arose independently at least four times and plant parasitism, three times. In addition, the investigators elucidated the relationship of *Caenorhabditis elegans* to major parasitic groups. This nematode model frequently is used in molecular biology. The success of this work allows more effective exploitation of genetic and biological knowledge of this model species.

The Picower Institute for Medical Research, Manhasset, New York, and the University of Dundee, Scotland, found that cimetidine, a histamine used to treat peptic ulcer, is also synergistic with the antimalarial drugs, chloroquine and pyrimethamine.

The University of Wisconsin TDRU, Linkage Genetics (United States), and the Ministry of Health, Trinidad and Tobago, used the techniques of amplified fragment length polymorphism and restriction fragment length polymorphism to study mosquito populations. The scientists reported that the restriction fragment length polymorphism was a DNA marker superior to dominant molecular markers in detecting the substructure of the *Aedes aegypti* population and in elucidating the influence of human activities (e.g., insecticide use) on genomic structure in the mosquito.

Tuberculosis

Colorado State University, Fort Collins, and the University of Wisconsin, Madison, have been investigating the role of *Mycobacterium tuberculosis* antigens in cell wall biogenesis. The scientists have now identified a carboxylesterase domain within the amino acid sequences of antigens 85A, B, and C. Each of these proteins acted as a mycolytransferase involved in the final stages of mycobacterial cell wall assembly. Furthermore, the use of an antagonist reversed this activity, demonstrating that these proteins are essential to cell wall assembly and that they may be targets for new antimycobacterial drugs.

The University of Espirito Santo, Vitória, Brazil, is a subcontractor on the study of clinical aspects of tuberculosis. During FY 98, the Case Western Reserve Tuberculosis Research Center completed the enrollment in a randomized, open-label, phase II clinical trial of multiple doses of an oral drug candidate. The investigators are treating tuberculosis with rifalazil, a rifampin derivative. The study is designed to test rifalazil's early antimycobacterial activity in combination with isoniazid, compared with isoniazid alone or with isoniazid plus rifampin. After 14 days, patients are switched to standard four-drug therapy with isoniazid, rifampin, pyrazinamide, and ethambutol. Rifalazil has a long half-life and has demonstrated high intracellular concentrations that might permit fewer doses and a shorter treatment period. In another open-label study, the investigators are using a multiple-dose protocol to test the safety and the early bactericidal activity of KRM-1648 in the treatment of adults with a new diagnosis of smear-positive pulmonary tuberculosis.

The Laboratory of Clinical Investigation (NIAID), New York University Medical Center and Rockefeller University, New York City, Cellgene Corporation, Warren, New Jersey, and Chiang Mai University and the Chiang Mai Anti-TB (tuberculosis) Association conducted a pilot study in Thailand. Findings suggested that thalidomide may contribute to weight gain and may reduce levels of tumor necrosis factor-α (TNF-α) and HIV-1 in HIV-1–positive patients with concomitant mycobacterial infection.

Case Western Reserve HIVNET is conducting a phase II study of the safety and preliminary evidence for microbiological and immunologic activity of recombinant human IL-2 in HIV-negative patients with tuberculosis in Uganda.

Vaccines

A large multicenter study supported by NIAID has shown that a new attenuated live virus vaccine, which is given in a nasal spray, is very effective in preventing influenza in healthy young children. Overall, the vaccine provided 93% protection. If these results are confirmed and the vaccine is licensed, it would be easier, faster, and less expensive to administer than an injection, especially in children.

NIAID-supported investigators at Yale University School of Medicine, New Haven, Connecticut, to participate in the Lyme Disease Vaccine Study Group, which conducted a multicenter, double-blind, randomized trial of more than 10,000 participants. The investigators evaluated the effectiveness of a SmithKline Beecham (United States) recombinant outer-surface lipoprotein A of *Borrelia burgdorferi* plus adjuvant vaccine (Lymerix). They found that the vaccine was safe and that, after three doses administered at study entry and 1 and 12 months later, it was 76% effective in preventing Lyme disease and 100% effective in preventing asymptomatic infection with *B. burgdorferi.* Yale University School of Medicine was also a member of the Recombinant Outer-Surface Protein A Lyme Vaccine Study Consortium, which evaluated a similar vaccine (Imulyme) that was given without adjuvant vaccine. That vaccine, manufactured by Pasteur-Merieux Connaught (United States) was administered at the same intervals and was 92% effective in preventing infection, as measured by clinical symptoms or seroconversion. The difference in the effectiveness of the vaccines may be due to the composition of the volunteer groups. Current efforts are focusing on evaluation of the vaccines in children, who are at highest risk for Lyme disease.

Scientists at the Laboratory of Persistent Viral Diseases (NIAID) and CDC's National Center for Infectious Diseases have developed a DNA-based candidate for rabies vaccine that protects cynomolgus monkeys against challenge with the live virus. An effective DNA-based rabies vaccine for humans would have the advantages of simple production, low cost, and heat stability, which would not require a cold chain (refrigeration).

The University of Maryland, Baltimore, and the Imperial College of Science, Technology, and Medicine, London, England, are examining (a) the safety of live oral *Salmonella typhi* vaccine strains with deletions in the htrA, aroC, and aroD genes and (b) the immune response they induce in humans. The vaccines were well tolerated, and they induced serum immune responses to *S. typhi* lipopolysaccharide and H antigens in 75%–100% of volunteers. Cells secreting *S. typhi*–specific cells were found in all volunteers, and 63%–83% developed lymphoproliferative responses to *S. typhi* flagellar and particulate antigens after higher doses. These studies demonstrated the potential of CVD 908-htrA as a live *S. typhi* vector for the delivery of heterologous genes, and a clinical trial of such a construct is being planned. In the course of these studies, the investigators found that some attenuated recombinant *Salmonella* vaccine vectors are lethal in mice that are deficient in IFN-γ. This finding raises concern about administration of these products to immunodeficient persons.

The Laboratory of Parasitic Diseases (NIAID) and Kenya Medical Research Institute, Kissian, determined that infants and their mothers mounted a similar response by producing a 19-kilodalton antibody to the merozoite surface protein but that the response in infants was short-lived. By 300 days of age, however, toddlers could mount a response equivalent to that of their mothers. In longitudinal, prospective studies, acquisition of immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody responses to the merozoite surface protein was associated with protection against fever and parasitemia in infants and pregnant women. These findings have implications for the development of vaccines against falciparum malaria, which produces more severe illness than other types of malaria in young children in Africa.

In a study in Mali, the University of Maryland, Baltimore, and the National Institute for Public Health Research, Bamako, determined that a single dose of the live oral CVD 103-HgR cholera vaccine was safe and immunogenic in both HIV-positive and HIV-negative adults.

NIAID is supporting investigators at the University of Maryland, Baltimore, to determine factors associated with the emergence of *Vibrio cholerae* 0139 in Peru. NIAID is also funding the university to perform a 2-year efficacy trial of the oral, inactivated, whole-cell plus recombinant cholera vaccine. Scientists from Universidad Peruana Cayetano Heredia and the U.S. Naval Medical Research Institute Detachment, Lima, evaluated a bivalent live oral cholera vaccine (CVD 103-HgR/CVD 111) in adult volunteers from Peru and the United States. The investigators concluded that it is feasible to produce a single-dose, oral, bivalent vaccine that is safe and immunogenic against both biotypes (El Tor and classical) and both serotypes (Inaba and Ogawa) of cholera, for populations in both developed and developing countries.

Mt. Sinai Medical Center and New York University, New York City, and the National Center of Biotechnology, Madrid, Spain, reported that recombinant influenza vaccine expressing a human malaria antigen can elicit potentially protective immune CD8+ T-cell responses in mice.

NIAID continues to fund the National Bacteriological Laboratory for research on long-term toxicity and efficacy of pertussis vaccines. The investigators are conducting follow-up of patients in a double-blind randomized trial to determine the efficacy of acellular pertussis vaccines compared with that of traditional whole-cell vaccines in children in Sweden. The initial trials, completed in 1996, showed that the acellular vaccines produced less toxicity and a better immune response. Three acellular pertussis vaccines have subsequently been licensed in the United States.

The Swiss Serum and Vaccine Institute, Basel, is cooperating with the University of Maryland Medical School, Baltimore, and the Naval Medical Center, Callao, and the U.S. Naval Medical Research Institute Detachment, Lima, Peru, to evaluate a bivalent CVD 103-HgR/CVD 111 live oral cholera vaccine in adult volunteers in the United States and Peru. Hoffmann-La Roche, Basel, is collaborating with the University of Alabama, Birmingham, and the University of Osaka, Japan, to describe and characterize the effects of cholera toxin on the immune system.

The University of Maryland School of

Medicine, Baltimore, and the U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Maryland, Walter Reed Army Institute of Research, Washington, D.C., and the Armed Forces Research Institute of Medical Research, Bangkok, Thailand, are carrying out expanded phase I studies of four monovalent dengue virus vaccines. Preliminary results show that the vaccines are appropriately attenuated for use in humans and can induce antibody in 40%–100% of the volunteers. Another facet of the study was to define any risk of transmitting the four dengue vaccines from volunteers with viremia to *Aedes aegypti* mosquitoes.

Under an NIAID contract, the University of Cincinnati, Ohio, is carrying out a virulent *Vibrio cholerae* 0139 challenge model and phase I and II vaccine trials in Thailand.

Rotavirus is the most prevalent cause of life-threatening diarrhea in infants and children younger than 2 years of age. In 1998, a quadrivalent oral rotavirus vaccine developed in rhesus monkeys by scientists in the Laboratory of Infectious Diseases (NIAID) reduced severe diarrheal illness by 88% in a study of more than 2,000 infants in Venezuela. The study was carried out by the Laboratory and the Central University of Venezuela, Caracas. This is the first large-scale study designed to determine whether the quadrivalent vaccine is effective in a developing country where rotavirus transmission is year round rather than seasonal, as it is in temperate climates. The vaccine was only 48% effective in preventing the first attack of rotavirus, but it had a significant effect in preventing serious dehydration (75%) and reduced hospital admissions (70%).

Viral Diseases

NIAID supports NCI (NIH), CDC, the Yerkes Primate Center, Atlanta, Georgia, and the University of Hawaii, Honolulu, to participate in a multicenter, international effort involving institutions in Belize, Central African Republic, France, and Indonesia. The investigators are studying the sequencing and evolution of the tax gene, for types I and II human and simian T-cell leukemia/lymphoma viruses (HTLV and STLV, respectively).

Researchers at the Laboratory of Infectious Diseases (NIAID), the Illinois Department of Agriculture, and Iowa State University, Ames, isolated the first strain of hepatitis E virus in a pig.

Colorado State University, Fort Collins, has engineered resistance in *Aedes aegypti* to a West African and a South American strain of yellow fever virus.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Argentina

University of Arizona International Cooperative Biodiversity Group Project. The University of Arizona, Tucson, is cooperating with the Institute of Biological Resources, Buenos Aires, and the National University of Patagonia to identify biological properties of arid-land plants in Argentina, for development of therapeutic agents.

University of New Mexico Emerging Virus Center. With the University of Pennsylvania, Kennett Square, New Mexico State University, Las Cruces, and the National University of Salta, Argentina, the University of New Mexico Emerging Virus Center found serological evidence of past infection with a sin nombre Hantavirus in 40.4% of Indians living in western Paraguay and 17.1% of Indians in the Salta Province of northern Argentina.

Bacterial Diseases. In FY 98, the University of Texas Medical School, Houston, the Foundation of the Center for Infectious Disease Studies, Buenos Aires, and the Center for Microbiological Research, Mendoza, reported the first isolation of vancomycin-resistant *Enterococcus faecium* in Argentina.

Australia

AIDS. The Macfarlane Burnet Center for Medical Research, Fairfield, determined that an in vivo mutation from leucine to tryptophan at position 210 in HIV-1 reverse transcriptase contributes to high-level drug resistance to 3'-azido-3'-deoxythymidine (AZT, zidovudine).

The University of New South Wales is an active member of the Tricontinental AIDS Cohort Study.

Parasitic Diseases. The Australia Genome Facility and the Walter and Eliza Hall Institute of Medical Research, Melbourne, are collaborating with Johns Hopkins University, Baltimore, Maryland, Case Western Reserve University, Cleveland, Ohio, the Papua New Guinea Institute of Medical Research, Goroka, and the Swiss Tropical Institute, to explore the genetic basis of severe anemia in falciparum malaria in a tribal group in Papua New Guinea.

Viral Diseases. The Victorian Infectious Disease Reference Laboratory, Fairfield, participates in the Atlanta Human Herpesvirus 8 (HHV-8) Working Group, which is investigating genetic variation of this recently described virus in a variety of geographic sites.

Immunology. Historically, NIAID has supported a broad range of projects at the Walter and Eliza Hall Institute of Medical Research, Melbourne, including foreign awards. One active foreign award supports exploration of the mechanisms of lymphocyte–antigen interactions.

The Picower Institute for Medical Research, Manhasset, New York, and Monash Medical School, Victoria, determined that TNF-α upregulates expression of renal migration inhibitory factor in crescentic glomerulonephritis in the rat.

Austria

AIDS. Stanford University Medical Center, California, Activated Cell Therapy, Inc. (United States), and ImmunoAG, Vienna, carried out a phase I clinical trial of therapy with HIV antigen pooled allogeneic and autologous dendritic cells in HIV-positive patients. The treatment was well tolerated and enhanced the immune response of patients with high CD4+ T-cell counts.

Immunology. Children's Hospital, Boston, Massachusetts, and Children's Hospital, Vienna, reported that intravenous immunoglobulin is significantly effective in allowing reduction of dosage in children with asthma that requires high dosage of steroids

Bangladesh

Johns Hopkins ICIDR. In addition to its work in Peru, the Johns Hopkins ICIDR is collaborating with the International Center for Diarrheal Disease Research (ICDDR), Dacca, on factors that influence secretion of gastric acid and enteric infection in Bangladesh.

Bacterial Diseases. In FY 98, NIAID made a new grant award to Stanford University, California, to collaborate with the ICDDR, Dacca, in study of the structure, regulation, and function of the EPS of *Vibrio cholerae* 01. Johns Hopkins University, Baltimore, Maryland, has a grant to study the epidemiology and ecology of *V. cholerae* in Bangladesh.

The NIAID-NASA Participating Agency Service Agreement was used to supplement grant awards to the University of Maryland for research on use of remote sensing to link selected climatic factors with plankton blooms and reactivation of latent *V. cholerae* in the Bay of Bengal.

Parasitic Diseases. Scientists at the University of Virginia, Charlottesville, and the ICDDR, Dacca, compared polymerase chain reaction (PCR), isoenzyme analysis, and antigen detection in the diagnosis of infection and found that the results of PCR and antigen detection were comparable. With scientists at TechLab, Inc., Blacksburg, Virginia, they found that 4.2% of urban children with diarrhea had *Entamoeba histolytica* and 6.5% had *Entamoeba dispar,* compared with 1.0% of rural children with *E. histolytica* and 7.0% with *E. dispar. Shigella dysenteriae* and *Shigella flexneri* were more frequent in children with *E. histolytica.* During FY 98, NIAID made a new grant award to the University of Virginia and the ICDDR, Dacca, to initiate field studies of immunity to amebiasis in Bangladesh.

Barbados

Immunology. Johns Hopkins School of Medicine, Baltimore, the University of the West Indies, Bridgetown, and the University of Copenhagen, Denmark, are investigating atopy to chromosome 12q markers observed in linkage analysis in an Afro-Caribbean population with asthma and high levels of total immunoglobulin E (IgE).

Belarus

Viral Diseases. CDC, the University of Wisconsin, Madison, and the Belarusian Research Institute of Epidemiology and Microbiology, Minsk, have completed the sequencing of the Lassa fever virus.

Belgium

AIDS. The University of Louisville, Kentucky, the University of Pennsylvania, Philadelphia, and the Free University of Brussels are defining the cellular basis for host resistance to HIV-1 in persons lacking functional cytokine coreceptor 5 (CCR5) genes. The University of Pennsylvania, Johns Hopkins School of Medicine, Baltimore, and the Free University of Brussels are studying the use of chemokine receptors, orphan receptors, and herpesvirus-encoded receptors by diverse HIV and SIV (simian immunodeficiency virus) strains.

Bellvitge Hospital, Brussels, is participating in a multicenter international trial of the safety and antiretroviral activity of 1592U89, a new reverse transcriptase inhibitor. The agent is being administered alone or in combination with AZT in HIV-positive patients with no previous antiretroviral treatment.

Belize

AIDS. American University of the Caribbean is participating in a multisite study of the evolution of human and simian retroviruses.

Bolivia

Emerging and Reemerging Infectious Diseases. NIAID is cosponsoring the International Training and Research in Emerging Infectious Disease Program awards of the Fogarty International Center to the University of California, Berkeley, and Universidad Major de los Andes, to provide international training in research on bacterial and enteric diseases, hepatitis C, drug resistance, and multidrug resistance.

Botswana

Bacterial Diseases. During FY 98, NIAID made a career award to an investigator at the University of California, Berkeley, which includes the study of rifampin-resistant tuberculosis in Botswana.

Brazil

NIAID-USAID AIDS Agreement. During FY 98, the results of a pilot study conducted by Federal University, Rio de Janeiro, Johns Hopkins University, Baltimore, and the Laboratory of Immunoregulation (NIAID) suggested that infection with both HIV and human T-cell leukemia/lymphoma virus type I (HTLV-I) may be associated with greater immune dysfunction than infection with only HIV, even in subjects having similar CD4+ T-cell counts. Nevertheless, HTLV-I infection does not increase HIV viral load in vivo. The findings also indicate that infection with both HIV and HTLV-I is strongly associated with myelopathy.

University of Texas Medical Branch/Galveston Emerging Virus Center. During FY 98, NIAID made a new research grant award to the University of Texas Medical Branch, Galveston, to cooperate with Instituto Evandro Chagas, Belém, on the ecology and molecular epidemiology of Oropouche virus in Brazil. This Center and the U.S. Naval Medical Research Institute Detachment, Lima, Peru, have compared isolates of Oropouche virus from Brazil with isolates from other endemic areas.

Johns Hopkins HIVNET. For the past 4 years, NIAID has supported a HIVNET award to Johns Hopkins University, Baltimore, to collaborate with the Laboratory of Immunoregulation (NIAID) and Federal University, Rio de Janeiro, on study of bisexual and heterosexual transmission of HIV/AIDS in an urban setting in Brazil. This HIVNET will be phased out and transferred to the University of Pittsburgh, Pennsylvania.

In prospective studies, the HIVNET has accumulated evidence that, in patients infected with both HIV and HTLV-I, outcomes related to HTLV-I infection may be accelerated without faster progression of the HIV-1 infection. Such patients have more severe myelopathy and higher CD4+ T-cell counts and no apparent clinical benefit.

In a Brazilian male and female cohort with follow-up in 1991–1995, there was no gender-related difference in the progression of immunodeficiency.

Harvard ICIDR. With the National Center for Genetic Resources and Biotechnology, Brasilia, the Harvard ICIDR found that polymorphisms of genes for mannose-binding lectin and the gene products have a significant effect on the clinical outcome of infection with *Leishmania chagasi* and that mannose-binding lectin can modulate the co-stimulatory function of macrophages infected with *L. chagasi.*

With cofunding from NASA, the ICIDR used data derived from remote sensing and geographic information systems to study epidemic visceral leishmaniasis in urban Teresina, Piauí. High prevalence was associated with high proportions of forests, mixed vegetation, secondary growth, and pasture (land cover) and with high proportions of wooded areas having sparse residential buildings and pasture (land use).

The ICIDR is conducting a clinical trial (a) of standard glucantime therapy compared with allopurinol to treat cutaneous leishmaniasis and (b) of the role of heat therapy and immunoadjuvant agents in the management of cutaneous leishmaniasis.

In collaboration with Walter Reed Army Institute of Research, Washington, D.C., and Federal University and the National Health Foundation, Mato Grosso, the ICIDR is attempting to use the genetic polymorphisms of *Plasmodium vivax* parasites in patients with relapse, as a tool to determine sensitivity to primaquine.

University of Texas Medical Branch/ Galveston ICIDR. This ICIDR is studying immunoregulation in human infection with *Schistosoma mansoni.* Another project focuses on the human immune response to defined schistosome antigens.

University of Virginia ICIDR. A major thrust of research at the University of Virginia ICIDR is to determine the role of cytokines and cellular immune determinants in persistent diarrhea in Brazilian patients at high risk for cryptosporidiosis, enteroaggregative *E. coli,* and other enteric infections. The ICIDR is investigating the mechanisms of action of enteroaggregative *E. coli* infection in intestinal inflammation and growth impairment and the potential role of a novel IL-8–releasing protein.

The ICIDR is collaborating with Federal University, Rio Grande do Norte, Natal, on study of the natural history and human immunogenetics of visceral leishmaniasis in the states of Cear(and Rio Grande do Norte.

Federal University/Bahia TMRC. This TMRC is studying the immunoregulation of human leishmaniasis, in particular, HLA and T-cell responses in patients infected with *S. mansoni* who develop hypersplenism.

AIDS. The University of California, Berkeley School of Public Health, the University of California, San Francisco, Irwin Memorial Blood Center, San Francisco, New York Blood Center, New York City, the University of Washington, Seattle, Adolfo Lutz Institute, São Paulo, Hemocentro de São Paulo, and the University of São Paulo found HIV-1 clade F in a significant number of injecting drug users.

Cornell Medical College, New York City, Federal University, Rio de Janeiro, the Adolfo Lutz Institute, the Emilio Ribas Infectious Disease Institute, and the Medical Division of the Penitentiary System, São Paulo, and the University of São Paulo conducted a prospective study of female penitentiary inmates with HIV infection and tuberculosis. Although the conversion rate for purified protein derivative was common (29% and 32%) in both groups, HIV-positive women had rates of clinical tuberculosis that were 10 times higher than those among HIV-negative women (9.9 vs. 0.7 cases per 100 prison years).

Bacterial Diseases. Emory University, Atlanta, Georgia, and Albert Einstein College of Medicine, Bronx, New York, collaborated with the National Research Institute of Amazonia, Manaus, to investigate an epidemic of tuberculosis with a high rate of negative tuberculin tests among a population of Yanomami Indians who had not been exposed to tuberculosis until recently. This Amerindian population had a diminished cell-mediated immune response and increased antibody responses, compared with those among populations having extensive previous exposure to tuberculosis. These findings suggest that tuberculosis may be a powerful selective pressure on human evolution, which over centuries has shaped the nature of human immune response to infection with tuberculosis.

Mycotic Diseases. Albert Einstein College of Medicine, Bronx, New York, and Federal University, Minas Gerais, found that L-743,872, a pneumocandin compound, enhanced the activities of amphotericin B and fluconazole against *Cryptococcus neoformans* in vitro.

Parasitic Diseases. NIAID provided funding to the Oswaldo Cruz Foundation (FIOCRUZ), Belo Horizonte, Federal University and the University of Vale do Rio Dolce, Minas Gerais, and the State University of Northern Flumenense, Rio de Janeiro, to collaborate with DNAX Research Institute, Palo Alto, California, to evaluate cytokines as determinants of resistance and pathology in human *S. mansoni* infection. Preliminary results indicate that IL-10 is important in regulating the immune response (and possibly in controlling morbidity) and that the production of IFN-γ may be associated with resistance to infection. CDC, DNAX Research Institute, Palo Alto, California, FIOCRUZ and Federal University, Belo Horizonte, the University of Vale do Rio Dolce, Minas Gerais, Valadares Governale, and the Faculty of Medicine of Triangulo Mineiro, Uberoi, are examining cytokine regulation of human immune response to *S. mansoni.* The investigators reported that IL-10 has an important role in modulation of the immune response in asymptomatic patients with chronic disease and that cytokine may also be an important factor in controlling morbidity.

Scientists at the Laboratory of Parasitic Diseases (NIAID) and Federal University, Minas Gerais, concluded that the opposing effects of nitric oxide, which protects against *Toxoplasma gondii* but at the same time limits the host immune response, contribute to establishment of a characteristic chronic state of host–parasite equilibrium.

The St. Louis University Health Sciences Center, Missouri, and Federal University, Rio de Janeiro, showed that recombinant cruzipain, a unique *Trypanosoma cruzi* cysteinyl proteinase, induces *T. cruzi*–specific responses of type 1 helper T (TH1) cells and mucosal immunoglobulin A (IgA).

Viral Diseases. Yale University School of Medicine, New Haven, Connecticut, is coordinating an international study on the origins of dengue virus type 2, which is associated with increased pathogenicity in the Americas. The study includes FIOCRUZ, Rio de Janeiro, and Instituto Evandro Chagas, Belém.

NIAID has awarded a new grant to the University of Texas Medical Branch, Galveston, to study the molecular epidemiology and ecology of Oropouche virus in Brazil.

Immunology. The University of Virginia, Charlottesville, and the Paulista School of Medicine, São Paulo, found that skin-prick tests containing an extract from *Blomia tropicalis* mites were positive in 93% of Brazilian children who were allergic to mites, compared with 90% of children with recombinant group 5 allergens. These results suggest that skin tests for recombinant *B. tropicalis* antigen, which are easier to administer, will be useful in the evaluation of children with allergic symptoms in tropical countries.

Vector Biology. The Laboratory of Parasitic Diseases (NIAID) and the State University of Northern Flumenense, Rio de Janeiro, reported that *Plasmodium* ookinetes preferentially invaded a previously unrecognized cell type in the mosquito midgut.

Cambodia

University of Washington STD Cooperative Research Center. This Center, CDC, the Ministry of Health, and the Reproductive Health Association of Cambodia have reported on the explosive spread of HIV-1 diseases and STDs.

Cameroon

Georgetown University ICIDR. Georgetown University ICIDR collaborates with the University of Yaoundé. The ICIDR is designed to provide information about the acquisition of immunity to malaria, which is expected to establish the scientific basis for development of candidates for protective vaccine. To this end, studies are conducted in the populations of four villages near Yaound(. The research will focus on (1) the effects of malaria on fetal development; (2) the acquisition of immunity to malaria in newborns; and (3) the acquisition of immunity to malaria in children and adults.

Family Health International Microbicide Study. Family Health International, Research Triangle Park, North Carolina, and the Ministry of Health, Cameroon, carried out a double-blind controlled clinical trial of contraceptive film impregnated or not impregnated with the spermicide nonoxynol 9, as a method of reducing STD and HIV transmission in female commercial sex workers in two cities. Both groups experienced a reduction in the rate of STD, but HIV transmission remained the same in both groups.

AIDS. The University of California, San Francisco, Pathogenesis, Inc. (United States), and the Southwest Foundation for Biomedical Research, San Antonio, Texas, conducted a study to determine the susceptibility of peripheral blood mononuclear cells from gorillas, orangutans, and baboons to an HIV-1 type O isolate from a Cameroon patient with AIDS. The results indicate that these endangered great apes could be infected with HIV-1.

Parasitic Diseases. NIAID has made a new grant award to the New York Blood Center, New York City, to investigate the protective immunity in humans against *Onchocerca volvulus* larvae.

Canada

University of New Mexico Emerging Virus Center. This Center is collaborating with the University of Alberta, Edmonton, and the University of Manitoba, Winnipeg, on a double-blind placebo-controlled trial of intravenous ribavirin as an antiviral treatment for presumed Hantavirus pulmonary syndrome.

University of Washington STD Cooperative Research Center. The University of Manitoba collaborates with the University of Washington STD Cooperative Research Center, Kenya.

AIDS. In FY 98, NIAID made a new foreign award to an investigator at the University of British Columbia, Vancouver, to perform a multidisciplinary study of acute HIV infection. The University of British Columbia is a member of the Tricontinental AIDS Cohort Study.

Bacterial Diseases. A new NIAID award to the University of Tennessee, Memphis, expands collaboration with the University of Toronto, Ontario, on the immunopathogenesis of group A streptococcal infections.

Harvard Medical School, Boston, Massachusetts, Baylor College of Medicine, Houston, Texas, and the National Research Council of Canada, Ottawa, Ontario, observed that directed coupling of type III group B streptococci to a carrier protein yielded a conjugate vaccine. The vaccine preserved expression of a highly labile conformational epitope involving sialic acid, and it enhanced immunogenicity compared with that provided by uncoupled capsular polysaccharides.

Parasitic Diseases. In a study at Chicago Medical School, Illinois, Temple University School of Medicine, Philadelphia, Pennsylvania, and the University of British Columbia, findings indicate that *Leishmania* surface protein glycoprotein 63 (gp63) contributes to the virulence of parasites by exerting a novel type of control over complement fixation.

Viral Diseases. The University of Minnesota, Minneapolis, and the University of Laval, Quebec City, Quebec, have determined that therapy with ganciclovir to induce immune response significantly decreased the viral DNA load in the leukocyte populations of patients with cytomegalovirus who had compromised immune systems. The University of Alabama, Birmingham, and the University of Alberta, Edmonton, are evaluating ganciclovir in a phase III study on the treatment of symptomatic congenital cytomegalovirus infections.

The University of Alabama, Birmingham, and the University of Alberta are also conducting a placebo-controlled phase III evaluation of suppressive therapy with oral acyclovir suspension after neonatal infection with herpes simplex virus (HSV) limited to the skin, eyes, and mouth. A second placebo-controlled phase III trial is investigating the efficacy of acyclovir in HSV infections of the central nervous system.

The University of Virginia, Charlottesville, the University of Alberta, and the University of Manitoba, Winnipeg, are carrying out a phase II study of the safety, efficacy, and antiviral effects of nebulized zanamivir in patients hospitalized with serious viral influenza infections.

Immunology. Harvard Medical School, Boston, the National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado, and McGill University, Montreal, Quebec, have provided the first evidence that expression of eotaxin is higher in asthmatic airways and that eotaxin is involved in the selective recruitment of eosinophils into the airways of patients with asthma.

Harvard Medical School and McGill University determined that eosinophils are the major source of synthesis and storage of eotaxin and MCP-4 in bullous pemphigoid disease.

In a study at the University of Michigan Medical School, Ann Arbor, Princeton University, New Jersey, the Medical College of Pennsylvania, Hershey, and Montreal General Hospital, findings indicate that constitutive secretion of IgG2b autoantibodies encoded by a *trans*-gene leads to symptoms of autoimmune diseases.

The National Institute of Child Health and Human Development (NIH), the National Jewish Center for Immunology and Respiratory Medicine, Denver, and McGill University reported that steroid-resistant asthma was associated with increased numbers of cells that expressed glucocorticoid receptor beta.

Central African Republic

AIDS. Institut Pasteur, Bangui, is a partner in an international project to examine the evolution of human and simian T-cell leukemia/lymphoma retroviruses.

The University of Washington, Seattle, and the Ministry of Health, Bangui, showed that vaginal douching with noncommercial preparations is associated with higher prevalence of HIV infection than is douching with commercial products.

Chile

Johns Hopkins ICIDR/Peru. The ICIDR is collaborating with the University of Arizona, Tucson, and Catholic University of Chile, Santiago, to study the effects of infection with *Cryptosporidium parvum* on the growth and development of Peruvian children. Results indicate that *C. parvum* has a lasting adverse effect on linear (height) growth, especially when the infection is acquired during infancy and when children have stunted growth before they become infected.

University of Maryland ICIDR. This ICIDR is evaluating the clinical acceptability and immunogenicity of CVD 103-HgR cholera vaccine in infants. In a related study, researchers are examining the effect of microbial overgrowth in the small bowel on the immunogenicity of the cholera vaccine in individuals.

Bacterial Diseases. Washington University School of Medicine, St. Louis, Missouri, and Catholic University of Chile, Santiago, found that PCR can be used to establish a reference standard for evaluating rapid tests for group A streptococcal infections in children who have pharyngitis. These tests are nearly as sensitive but less specific than culture on blood agar.

Parasitic Diseases. St. Jude Children's Research Hospital, Memphis, Tennessee, and the University of Chile Medical School and the Medical Legal Institute Hospital, Santiago, conducted a case–control study that showed a strong association between *Pneumocystis carinii* infection and sudden infant death syndrome in Chile.

China

Institute of Parasitology TMRC. This award directly funds the Institute of Parasitology, Chinese Academy of Preventive Medicine, Shanghai, to take advantage of the research opportunities related to construction of the Yangtze River Dam. The TMRC is obtaining preconstruction baseline data, is determining the dam's effect on human health, and plans to develop new or improved prevention tools, including vaccines.

Specifically, the TMRC will establish a core of geographic information systems and resources for collection of parasites; study the genetic diversity of hookworms, to develop a candidate recombinant vaccine; determine the genetic diversity of *Schistosoma japonicum* (schistosomiasis) and *Paragonimus* (paragonimiasis) as a prelude to identifying vaccine candidates; and define the biogeography and genetic diversity of the snail vectors that transmit *Schistosoma* and *Paragonimus*.

Hookworm infection. Hookworm infection and disease are widespread in China and are particularly prevalent in the Yangtze River Basin, where an estimated 194 million people are infected with *Ancyclostoma duodenale, Necator americanus,* or both helminths and where there are up to 50 million cases of hookworm anemia. In cooperation with Yale University School of Medicine, New Haven, Connecticut, the TMRC is examining two recombinant vaccine candidates cloned from *Ancyclostoma caninum.* These candidate vaccines are directed against either the infective larval stage or the adult intestinal stage of the organism, which feeds on blood. The candidate vaccines will initially be evaluated in the *A. caninum* dog model set up at Yale University School of Medicine.

Schistosomiasis. One focus in this TMRC project is to develop two types of molecular vaccines for *Schistosoma japonicum* by using either recombinant polypeptides or plasmid (naked) DNA. The scientists will examine a number of candidate cDNAs (complementary DNAs), their expressed polypeptides, or both, including a particularly promising *S. japonicum* glutathione-*S*-transferase. Concurrently, the TMRC will collect molecular genetic data from Chinese strains of *S. japonicum,* to detect intraspecific genetic diversity and to carry out surveillance for the emergence or reemergence of new schistosome species in China. The TMRC is studying the effect of treating water buffalo, which are an animal reservoir, on the incidence of human infection and disease due to S. japonicum.

Medical malacology. The objectives of this TMRC project are to uncover the species diversity of snails in the Yangtze River drainage area and the diversity of species of *Schistosoma* and *Paragonimus,* which have evolved together with the snails over the past 10–14 million years.

AIDS. The University of Hawaii, Manoa, Oahu, the University of California, Los Angeles, and the National Center for AIDS Prevention and Control, Beijing, have completed sequencing of the nef gene of HIV-1 subtype B from professional plasma donors in China.

Bacterial Diseases. A clinical researcher in the Laboratory of Host Defenses (NIAID), in efforts to prevent an epidemic, provided assistance to Shenzhan Hospital to control a nosocomial outbreak of *Mycobacterium abscessus* in patients, after surgical procedures.

Rocky Mountain Laboratories (NIAID), CDC, Yunnan Provincial Institute of Epidemic Disease Control and Research, Dali, and the Chinese Base for Control and Treatment of Plague and Brucellosis, Baiching, have identified a cryptic 19-kilobase plasmid, which is the dimer of the 9.5-kilobase plasmid associated with U.S. isolates of *Yersinia pestis.*

Parasitic Diseases. The Laboratory of Parasitic Diseases (NIAID) is collaborating with the Hong Kong Institute of Biotechnology, Ltd., on the development of a candidate vaccine for gametocyte malaria.

Viral Diseases. St. Jude Children's Research Hospital, Memphis, detected avian influenza virus in pigs from China. Investigators are working (1) to determine whether pigs are a risk factor in the genesis of human pandemic influenza; (2) to predict whether avian influenza viruses in pigs in China could become the precursors of the next human pandemic; (3) to establish which molecular changes are associated with transmission of avian influenza to mammalian hosts; and (4) to use this information in developing epidemiologic probes for detection of the virus.

Immunology. In a study at the University of California, Davis, and the Chinese University of Hong Kong, findings suggest that tropomyosin is the common allergen in crustaceans and mollusks.

Colombia

University of Texas Medical Branch/Galveston Emerging Viruses Center. This Center and the National Institute of Health, Bogotá, have captured and identified several species of *Culex* (subgenus *Melanoconion*) in an enzootic focus of Venezuelan equine encephalitis in the middle Magdalena Valley in Santander. These mosquitoes may be insect vectors.

International Center for Research and Training in Medical Sciences/Cali TMRC. Funding for this TMRC was discontinued in FY 97, but publications continue to appear. The TMRC studied host–parasite–vector relationships in experimental *Leishmania chagasi* infections of *Didelphis marsupialis.* Findings suggest that this mammal may be an important reservoir for maintenance of *L. chagasi* in the endemic foci in northern Colombia.

Viral Diseases. The Universidad del Valle, Cali, is participating in an NIAID-funded study on the origins of dengue virus type 2 in the Americas. This type of the virus is associated with increased pathogenicity.

Immunology. The University of Cartagena participates in an NIAID-supported international study of the genetics of asthma, atopy, and the linkage of HLA to mite-sensitive asthma. The University of South Florida, Tampa Bay, Johns Hopkins School of Medicine, Baltimore, Maryland, and the University of Cartagena have identified and characterized a recombinant protein that appears to be a major allergen of the mite *Blomia tropicalis.*

Vector Biology. In FY 98, NIAID competitively renewed a grant to Yale University, New Haven, to continue collaboration with the National Institute of Health, Colombia, on the genetics and biogeography of sand fly vectors of human disease in Colombia and elsewhere in Latin America.

Costa Rica

Immunology. The University of California, Los Angeles, Virginia Mason Research Center, Seattle, Washington, and Hospital Nacional de Niños, San José, are using reverse transcriptase PCR to detect ataxia-telangiectasia mutations in different ethnic populations.

Côte d'Ivoire

AIDS. The University of California, San Francisco, Pathogenesis (United States), and the Southwest Foundation for Biomedical Research, San Antonio, Texas, performed a study to determine the susceptibility of peripheral blood mononuclear cells from gorillas, orangutans, and baboons to human immunodeficiency virus type 2 (HIV-2) isolates obtained from patients in Côte d'Ivoire.

Côte d'Ivoire is participating in an international study to compare cesarean section versus vaginal cleansing with chlorhexidine benzochromium chloride to reduce the intrapartum transmission of HIV-1 from mother to newborn.

Parasitic Diseases. Researchers at the University of Alabama, Birmingham, and the WHO Onchocerciasis Control Program, Bouaké, have concluded that the two *Onchocerca volvulus* filarial parasite strains and the six *Simulium damnosum senso* lato black fly species prevalent in West Africa do not have a role in the biology of onchocerciasis transmission.

Vector Biology. The University of Alabama, Birmingham, and Institut Pierre Richet, Bouaké, have used molecular biology techniques to identify whether humans or animals were the source of the blood meal of tsetse flies, the vectors of African trypanosomiasis.

Czech Republic

Bacterial Diseases. The University of Texas Southwestern Medical Branch, Dallas, and the Institute of Hematology and Blood Transfusion, Prague, have shown that binding of heme–hemopexin complexes by soluble HxuA protein allows *Haemophilus influenzae* to use this complexed heme.

Denmark

Immunology. Johns Hopkins University, Baltimore, and NeuroSearch A/S, Glastrop, have confirmed that pockets in the antigen–peptide-binding groove (H-2Kb) have a role in determining peptide-binding affinity and specificity. This finding suggests that these characteristics may be determined by changes in the orientation of side chains.

Dominican Republic

AIDS. The University of Washington, Seattle, Seattle-King County Health Department, Family Health International, Arlington, Virginia, and the Institute of Dermatology and the National Health Center, Santo Domingo, determined that syphilis, sexual practices, and commercial sex were associated with HIV infection, rather than sexual identity per se, in homosexual men in the Dominican Republic.

Ecuador

Parasitic Diseases. The Laboratory of Parasitic Diseases (NIAID) and Hospital Voz Andes, Quito, reported that human infection with *Onchocerca volvulus* does not affect the helper T-cell phenotype of the cellular immune response to mycobacterial antigen. These scientists and others, from the University of Edinburgh, Scotland, determined that levels of RANTES, a chemokine, correlated negatively with the severity of the rash and lymphedema associated with adverse drug reactions in the treatment of onchocerciasis. The findings suggest that circulating RANTES may contribute to modulation of eosinophil expression in vivo.

Egypt

University of Minnesota ICIDR. This ICIDR is collaborating with El Hussain University, Cairo, in research on the serum IgM antibody response to the galactose-inhibitable adherence lectin of *Entamoeba histolytica.*

The ICIDR is collaborating with El Hussain University Hospital, Cairo, on a prospective study of *E. histolytica* and *E. dispar* after cure of amebic liver abscess. The researchers showed for the first time that patients cured of amebic liver abscess possess immunity to *E. dispar* intestinal infection.

Washington University ICIDR. This ICIDR has identified and is now evaluating circulating parasite antigens in persons with human filariasis infections in the Nile Delta.

Bancroftian filariasis is resurgent in the Nile Delta, and the ICIDR is carrying out a longitudinal study of the disease in a cluster of five closely spaced villages outside Cairo. The purpose of the investigation is to identify risk factors for infection and to improve understanding of immunity to human filariasis. An ELISA developed for the antigen has proved to be much more sensitive than the traditional examination of a nighttime blood smear in determining the prevalence of infection. The decline of infection intensity and antigen levels with age suggests that humans develop a degree of immunity to *Wuchereria bancrofti* infection after many years of exposure. The project has developed a new, scientifically based strategy for filariasis control based on (1) selective diagnosis of sentinel populations to identify areas where the disease is endemic and (2) repeated, annual mass treatment with new, more effective, single-dose combination regimens in entire populations in endemic areas.

With ICT Diagnostics, Australia, the ICIDR field tested a rapid card test for filarial antigen and found it both sensitive and specific for *W. bancrofti* infection.

Bacterial Diseases. NIAID provides partial funding through the University of California, San Francisco, for four multidisciplinary projects to compare oral azithromycin with standard topical tetracycline for control of trachoma in community-wide treatment regimens. The University of California, San Francisco, Pfizer International, Inc., New York City, New York, and the University of Alexandria compared oral azithromycin with the topical oxytetracycline-polymyxin ointment recommended by WHO. The investigators found that one to six doses of azithromycin were equivalent to 30 days of daily application of the ointment, in the treatment and control of endemic trachoma in children in Egypt.

Parasitic Diseases. Smith College, Northampton, Massachusetts, and Ain Shams University, Heliopolis, have successfully adapted PCR and PCR-ELISA techniques in a new test to detect *W. bancrofti.* These techniques are sensitive for the detection of this filarial parasite in infected patients. Although the test is not specific for *W. bancrofti,* it may prove useful because of its sensitivity in detecting this diurnal parasite in daytime blood specimens or indirectly in the urine.

Case Western Reserve University, Cleveland, Ohio, Hoffmann-La Roche, Nutley, New Jersey, and Assiut University demonstrated that IL-12 modulates IgE production driven by helminth antigen. This modulation is partly due to regulation of the relative quantities of IFN-γ and IL-4 generated by antigen-specific lymphocytes.

During FY 98, NIAID made a new award to Case Western Reserve University to collaborate with Cairo University in a study of the genetic aspects of hepatic fibrosis associated with schistosomiasis in Egypt, where the prevalence is high, and in Kenya, where it is low.

The University of Lowell, Massachusetts, Michigan State University, East Lansing, and Al Azar University, Cairo, have examined isolates of *Schistosoma mansoni* from patients who were not cured after three successive doses of praziquantel. The investigators found that, in three of nine patients, the organism had lower drug sensitivity than in control subjects. Michigan State University and Al Azar University reported that an extract of myrrh, an oleo-gum resin from the plant *Commiphora molmol,* was safe and effective in the treatment of patients with intestinal *S. mansoni* infection. Patients treated with three daily doses of the myrrh extract showed a reduction in elevated levels of liver enzymes and a 98% reduction in worm load. There were also reductions in the percent of patients with ulcers (from 56% to 3.2%) and in the percent of patients with distal polyps (from 19% to 8.1%). In FY 98, NIAID made a new grant award to Michigan State University to study the emerging problem of *S. mansoni* resistance to praziquantel.

The State University of New York, Buffalo, and Ain Shams University, Heliopolis, have characterized Sm20.8, a member of a family of schistosome tegmental antigens. This antigen shows immune reactivity with sera from infected rabbits and humans vaccinated with irradiated cercariae.

Viral Diseases. The Laboratory of Infectious Diseases (NIAID), the University of Maryland, Baltimore, Assiut University, Mina University, and American University of Cairo, Egypt, and WHO, Geneva, Switzerland, studied the epidemiology of hepatitis C virus (HCV) in a population 30 years of age or younger in a village in Upper Egypt. HCV was more prevalent in males (11.3%) than in females (6.5%) and was significantly associated with blood transfusions, dental manipulations, and medical injections, but not with concurrent schistosomiasis.

Immunology. The University of Pennsylvania, Hershey, Virginia Commonwealth University, Richmond, and Al Azar University, Cairo, have used histochemical techniques with monoclonal antibodies to detect human basophils in late-phase allergic skin reactions.

Ethiopia

Parasitic Diseases. Louisiana State University, Baton Rouge, was awarded a small grant to apply global information systems technology to mapping the distribution of schistosomiasis in Ethiopia.

Finland

AIDS. Aurora Hospital, Helsinki, participates in multicountry projects to study the international epidemiology of disseminated *Mycobacterium avium-intracellulare* in AIDS and to evaluate the risks and benefits of BCG immunization in adults with AIDS. Results indicate that institutional systems that use recirculating heated hot water (e.g., indoor pools) are a risk factor for *M. avium-intracellulare* in Finland.

Bacterial Diseases. Stanford University, California, the University of Helsinki, and the National Public Health Institute, Turku, compared oral versus parenteral vaccination against *Salmonella typhi* Ty21a antigen. The researchers concluded that the site of antigen encounter determines the homing potential of human circulating lymphocytes.

Immunology. The University of California, San Francisco, and the University of Helsinki determined that, although both malignant and benign prostate glandular cells secrete CD46, CD55, and CD59, functionally, CD59 is the most important regulator of complement in prostatic cells.

France

University of Wisconsin TDRU. This TDRU is working with the Institute of Molecular and Cellular Biology, Strasbourg, to obtain DNA clones of inducible immune peptides and polypeptides from *Aedes aegypti* mosquitoes.

University of Mali TMRC. The Nutrition and Food Scientific and Technical Institute, Paris, is collaborating with this TMRC on the relationships of hemoglobins S and C and iron supplementation with malaria in Malian schoolchildren.

AIDS. City of Hope, Duarte, California, the California State Polytechnic University, Pomona, and Montpellier Institute of Molecular Genetics are monitoring retroviral RNA dimerization in vivo via ribozyme cleavage.

The Veterans Affairs Medical Center, Manhattan, and New York University, New York City, the University of Pennsylvania, Philadelphia, and Institut Pasteur, Paris, discovered that HIV envelope binds to the chemokine receptor CXCR4 independently of CD4 and that this binding can be enhanced by interaction with soluble CD4 or by HIV envelope deglycosylation.

The University of Alabama, Birmingham, and Institut Pasteur, Paris, found that the immune response to HIV clade B virus was not sufficient to prevent intravenous infection with a clade E strain, but it did restrict replication of the second virus after exposure by the mucosal route.

Children's Hospital, Wistar Institute of Anatomy and Biology, and the Hospital of the University of Pennsylvania, Philadelphia, and Institut Gustave Roussy, Villejuif, reported differential production of IL-10 during infection. The finding indicates that production of this cytokine is more complex than was previously thought and may depend on the infecting virus and other factors.

Institut Pasteur, Paris, participates in an international initiative to study the tax gene sequences from divergent monophyletic lineages of HTLV and STLV.

Harvard Medical School, Boston, Massachusetts, and Institut National de la Santé et de la Recherche Médicale (INSERM), Clamart, determined that early cytokine and chemokine gene expression in lymph nodes of macaque monkeys infected with SIV is predictive of disease outcome and vaccine efficacy.

DAIDS (NIAID), Walter Reed Army Institute of Research, Washington, D.C., Johns Hopkins University, Baltimore, St. Louis University School of Medicine, Missouri, New York University, the University of Washington, Seattle, Chiron Corporation, San Francisco, California, and Pasteur-Merieux, Connaught Laboratories, Marnes-les-Coquette, neutralized a clade B primary isolate by using sera from volunteers with HIV who received a recombinant gp120 vaccine. Johns Hopkins University, Duke University Medical Center, Durham, North Carolina, the University of Washington, Chiron Vaccines, Emeryville, California, and Pasteur-Merieux, Connaught Laboratories, Marnes-les-Coquette, reported that HIV-1 vaccines based on clade B elicited cross-clade reactivities in cytotoxic T lymphocytes from HIV-negative volunteers.

Virogenetics, Albany, New York, and Duke University Medical Center are collaborating with the AGIS group supported by ANRS groups in France, to study the safety and immunogenicity of a live recombinant canarypox virus vaccine expressing gp120, gag protein, and protease, boosted by a p24E-V3 peptide.

DAIDS (NIAID), the State University of New York, Stony Brook, Claude Bernard Hospital, Paris, and the University of Bordeaux reported that, in HIV-positive patients with CD4+ T-cell counts less than 200 x 101^6/L, an IgG anti-*Toxoplasma* antibody titer higher than 150 IU/mL was prognostic for development of toxoplasmic encephalitis. These investigators, together with investigators at Hospital Saint André and Hospital Pellegrin-Tripod, Bordeaux, determined that older age and a low CD4+ T-cell count were associated with survival after AIDS-defining events in HIV-positive patients with less than 200 CD4+ T cells, who were also positive for toxoplasmosis antibody.

Bacterial Diseases. University Louis Pasteur, Strasbourg, collaborated with the University of California, Davis, and the California Department of Fish and Game in the isolation of *Bartonella* spp. from California wildlife.

The University of California, Berkeley, and Institut Pasteur, Paris, have studied the active efflux of different antibiotics in wild-type strains of *Enterococcus* that are intrinsically resistant to numerous antimicrobial agents.

Parasitic Diseases. The Laboratory of Parasitic Diseases (NIAID) and CNRS, Strasbourg, reported that insect defensins (antimicrobial peptides) differentially killed some mosquito species that carry *Plasmodium gallinaceum.* Researchers at Dartmouth Medical School, Hanover, New Hampshire, and the National Institute of Agricultural Research's Training and Research Group in Pharmaceutical Sciences, Tours, showed that adoptive transfer of intraepithelial lymphocytes in the mouse gut protected against infection with *Toxoplasma gondii.*

Viral Diseases. Yale University School of Medicine, New Haven, the University of Georgia, Athens, and INSERM and Merieux Laboratories, Lyon, showed that a novel thymidine analogue (1'-fluoro-5-methyl-β-L-arabinofuranosyluracil) inhibited incorporation of dextroadenosine monophosphate in the viral DNA primer of duck hepatitis B virus (HBV).

Immunology. Harvard Medical School, Boston, and the Institute of Molecular and Cellular Biology, Strasbourg, identified and characterized croquemort, a novel *Drosophila* hemocyte and macrophage receptor that recognizes apoptotic cells.

Institut Pasteur, Paris, is a participant in the NIAID-funded international study of HLA and its association with mite-induced asthma.

French Guiana

University of Texas Medical Branch/Galveston Emerging Viruses Center. Institut Pasteur, Cayenne, the International Center for Agricultural Research for Development, Kouro, and the Group for Applied Military Service, Saint Laurent du Maroni, isolated, identified, and determined the seroprevalence of Mayaro virus fever in French Guiana.

Gabon

AIDS. Centre International de Recherche Médicale, Franceville, is participating with the University of Alabama, Birmingham, and New York University in an international consortium that is characterizing and titrating stock for challenge with an HIV-1 subtype E from chimpanzees. The University of California, San Francisco, the Southwest Foundation for Medical Research, San Francisco, and Pharmagenesis (United States) performed a study of the susceptibility of mononuclear cells from gorillas, orangutans, and baboons to an SIV isolate from wild-caught chimpanzees in Gabon.

The Gambia

AIDS. The University of California, San Francisco, the Southwest Foundation for Biomedical Research, San Antonio, Texas, and Pharmagenesis (United States) performed a study of the susceptibility of peripheral blood mononuclear cells from gorillas, orangutans, and baboons to HIV-2 isolates from patients in the Gambia.

Bacterial Diseases. NIAID supports an overseas contract with the London School of Hygiene and Tropical Medicine, England, and the Medical Research Council, the Gambia, for a phase I–II study of the safety and efficacy of combining a nona-valent pneumococcal conjugate designed for use in Africa with either a conjugate of diphtheria–pertussis–tetanus and *Haemophilus influenzae* type B vaccine or a meningococcal C conjugate vaccine in the same syringe.

NIAID also funds the University of California, San Francisco, for community-based treatment studies in the Gambia to compare single-dose oral therapy using azithromycin with WHO-recommended topical tetracycline eye ointment administered over an extended period, to control blinding trachoma.

Viral Diseases. During FY 98, a foreign award to the Medical Research Council, London, England, to study responses of cytotoxic T lymphocytes to measles in children in the Gambia expired.

Germany

AIDS. The German Primate Center, Göttingen, and Rockefeller University, New York City, are involved in a multicountry study using different clade B HIV-1 envelope from chimeric HIV and SIV in vitro and in vivo to infect *Macaca mulatta* monkeys. Beth Israel-Deaconess Medical Center, Dana-Farber Cancer Institute, Boston, Massachusetts, and the Bernard-Nocht Institute for Tropical Medicine, Hamburg, have documented that the envelope glycoprotein of HIV-1 does not selectively expand or deplete the V-H3 repertoire of primate B cells during acute AIDS infection. This finding is contrary to the prediction of the gp120 superantigen hypothesis.

The University of Alabama, Birmingham, the University of Wisconsin, Madison, and Freiburg University Hospital found that the constitutive responsiveness of gamma/delta T lymphocytes to Daudi-stimulated lymphocytes and monoethyl pyrophosphate is severely altered in HIV-positive persons.

Tufts University School of Medicine and New England Medical Center, Boston, Massachusetts, and the University of Munich showed that rolipram, a specific type IV phosphodiesterase inhibitor, also is a potent inhibitor of HIV-1 replication in vitro. Massachusetts General Hospital, Boston, and the University of Würzburg discovered that pentoxifylline, another phosphodiesterase inhibitor, reduced the cytoxicity of and cytokine release by CD8+, HIV-specific cytotoxic T lymphocytes.

Bacterial Diseases. The Laboratory of Immunoregulation (NIAID), NCI (NIH), and the Max Planck Institute for Immunobiology, Freiburg, discovered that *Borrelia burgdorferi* activates nuclear factor kappa-beta and is a potent inducer of expression of genes encoding for chemokines and adhesion molecules in endothelial cells and fibroblasts. Kendle/gmi, Munich, is in partnership with SmithKline Beecham Pharmaceuticals, Yale University School of Medicine, New Haven, and New York Medical College in evaluating the efficacy of vaccination against Lyme disease with a recombinant outer-surface protein A from *B. burgdorferi* and adjuvant vaccine.

The University of California, Los Angeles, Northwestern Healthcare Research Institute, Evanston, Illinois, Harvard Medical School, Boston, Albert Einstein College of Medicine, Bronx, New York, and the University of Erlangen reported that the ability of cytotoxic T cells to kill *Mycobacterium tuberculosis* depends on the presence of granulysin. This finding defines a mechanism by which T cells directly contribute to immunity against an intracellular pathogen.

Viral Diseases. Scripps Research Institute, La Jolla, California, and the University of the Saarland, Homburg, detected Borna disease virus and RNA in psychiatric patients, suggesting that this animal virus may cause human disease.

Rush Medical College, Chicago, Illinois, Case Western Reserve University, Cleveland, Ohio, and Boehringer Mannheim, Penzberg, found that infection with hepatitis G virus (HGV) was prevalent (26%) but produced no symptoms in HIV-positive patients in Cleveland.

Immunology. Johns Hopkins School of Medicine, Baltimore, is collaborating with the German Multicenter Allergy Study in Berlin, Düsseldorf, Freiburg, and Mainz, by analyzing evidence that chromosome 12q15–q24.1 markers are linked with high levels of total serum IgE.

The Max Planck Institute for Molecular Biology, Freiburg, is collaborating with Indiana University, Indianapolis, Harvard School of Public Health, Boston, and Baylor College of Medicine, Houston, Texas, on the role of cytokines in acute lung injury.

The Picower Institute for Medical Research, Manhasset, New York, and Phillips University, Marburg, found that macrophage migration inhibitory factor of pancreatic islet cells is glucose dependent, regulates insulin production, and may be important in carbohydrate metabolism.

Ghana

Parasitic Diseases. The University of Florida, Gainesville, is collaborating with Kumasi Hospital in the evaluation of therapy with dichloroacetate to correct the lactic acidosis in children with severe malaria.

Greece

Immunology. The University of Maryland School of Medicine, Baltimore, and Athens University Medical School are evaluating the implication, for immunotherapy, of the expression of CD28, CTLA4, CD80, and CD86 molecules in patients with autoimmune rheumatic disorders.

Haiti

Cornell Medical College HIVNET. This HIVNET supports collaboration between Cornell Medical College, New York City, Vanderbilt University, Nashville, Tennessee, and the National Research Laboratory and the Haitian Study Group on Kaposi's Sarcoma and Opportunistic Infections, Port-au-Prince, to conduct epidemiologic and clinical and prospective studies of HIV/AIDS and its manifestations in children and in couples discordant for HIV infection.

Children. Haitian children with HIV demonstrate rapid progression to symptomatic disease and death. The clinical presentation of pediatric HIV in Haiti differs from that in the United States. It is much more common for patients in Haiti to have signs of malnutrition, failure to thrive, and tuberculosis.

Discordant couples. In an ongoing study of discordant couples, the HIVNET determined that counseling and the provision of free condoms contributed to the institution of safe sex practices or abstinence in 45% of heterosexual discordant couples. Disappointingly, in the 55% of couples continuing to have unprotected sexual activity, the incidence of HIV transmission was 6.8% per 100 person-years.

Hungary

Bacterial Diseases. The University of Wisconsin, Madison, the University of Maryland School of Medicine, Baltimore, and the Biological Research Center, Szeged, characterized the molecular evolution of a pathogenicity island from a strain of enterohemorrhagic *E. coli* O157:H7.

Rockefeller University, New York City, and the National Institute of Hygiene, Budapest, identified and characterized a unique, epidemic, methicillin-resistant *Staphylococcus aureus* clone in Hungary.

Rockefeller University reported that 70% of pneumococcal isolates from Hungary are resistant to penicillin.

India

The Indo-U.S. Vaccine Action Program celebrated its 10th anniversary in 1998. During FY 98, NIAID received a $2 million gift to its Restricted Gift Fund by the Starr Foundation to support the Indo-U.S. Vaccine Action Program. Under the terms of the gift, these funds will be used to provide small (R03) grants and grant supplements up to $50,000 a year for a maximum of 3 years over the next 4 years.

Johns Hopkins HIVNET. This HIVNET supports Johns Hopkins School of Medicine, Baltimore, to collaborate with the Laboratory of Immunoregulation (NIAID) and the National AIDS Research Institute, Pune, which is under India's International Centers for Medical Research Program. The investigators are studying HIV-1, HIV-2, and STDs in heterosexual populations. During FY 97, this HIVNET did not compete successfully for renewal and will be phased out. A number of its activities, however, are expected to continue under individual NIH grant awards.

Pathogenesis. The HIVNET received support to study the pathogenesis of acute primary infection with HIV-1 subtypes prevalent in Pune.

Risk factors. The HIVNET documented in India that HIV-1 DNA is shed in secretions from genital ulcers. Shedding was significantly associated with the diagnosis of chancroid, genital ulcer disease for more than 10 days, and concurrent cervicitis or urethritis.

STD clinics. The HIVNET is carrying out a prospective cohort study of HIV seroincidence and risk factors for seroconversion in STD clinic patients in Pune. After more than 500 person-years of follow-up, the overall seroincidence was 10.0% per person-year. The highest incidence (22.8%) was in female commercial sex workers, followed by the incidence for males (8.9%) and that for female noncommercial sex workers (3.0%). Among these groups, the incidence was higher in younger patients and those with recurrent genital ulcer disease, urethritis, or cervicitis.

Prevention. The HIVNET is undertaking a phase I trial in Pune to increase condom use by couples discordant for HIV.

AIDS. During FY 98, NIAID made a new grant award to the principal investigator of the Johns Hopkins HIVNET site in Pune, to continue collaboration in research on the pathogenesis of acute primary HIV infection in India.

Bacterial Diseases. The University of Maryland, Baltimore, and NASA have used remote sensing techniques for indirect measurements of concentrations of *Vibrio cholerae* in the Bay of Bengal.

Viral Diseases. The Laboratory of Infectious Diseases (NIAID), CDC, and the All India Institute of Medical Sciences, New Delhi, are investigating the reactogenicity and immunogenicity of candidates for live attenuated 116E rotavirus vaccine.

Immunology. The Laboratory of Immunology and the Laboratory of Allergic Diseases (NIAID) and the Indian Institute of Science, Bangalore, identified a novel hydroxyproline-rich glycoprotein as the major allergen in *Parthenium* pollen.

Indonesia

AIDS. The U.S. Naval Medical Research Unit, Jakarta, and Bogor Agricultural University are involved in a large multicenter study of the tax gene sequences from monophylogenic types 1 and 2 of human and monkey leukemia/lymphoma retroviruses.

Viral Diseases. The University of Nebraska, Omaha, Murdoch University, Australia, and the Disease Investigation Unit, Denspassai, characterized the *cis-* and *trans*-regulatory elements in the long terminal repeater domain of the virus that causes Jembrana disease. This organism is a recently identified bovine lentivirus closely related to bovine immunodeficiency virus.

Ireland

AIDS. Boston University School of Medicine and Roxbury Community Center, Massachusetts, and Mater Misericordiae Hospital, Dublin, conducted a retrospective study of patients with HIV/AIDS in Boston. The study showed that Kaposi's sarcoma occurred in 3.6% of women compared with 9.9% of men.

Israel

University of Washington Hepatitis C Center. Investigators at this Center, the University of Illinois, Chicago, Santa Fe Institute and Los Alamos National Laboratory, New Mexico, and Bar-Ilan University, Ramat Gan, studied the dynamics of HCV infection and therapy with IFN-α in vivo. Findings suggest that early monitoring of viral load may help to guide antiviral therapy.

Columbia University ICIDR. The focus of the ICIDR is to study *Cryptosporidium, E. coli,* and *Giardia lamblia* infections in Arab and Jewish children in Israel.

Hebrew University of Jerusalem MERC. Scientists on this Middle Eastern Regional Contract (MERC) identified incongruities between leishmanial excreted factor and lipophosphoglycan serotypes in relation to the dissemination patterns of amastigotes that were associated with unusual sites of infection.

Working with Merhav Veterinary Clinic, Nataf, and Nature Reserve Authorities, Eilat, the MERC has documented the recent emergence of visceral leishmaniasis in humans and domestic dogs in central Israel. The presence of seropositivity in wild jackals (6.7%) and red foxes (5.0%) and the reappearance of the jackal population after near extinction suggest that wild canids may be important in the spread of this life-threatening infection.

AIDS. The Hadassah Medical School, Jerusalem, and the Laboratory of Viral Diseases (NIAID) showed that the immunogenicity of recombinant vaccinia viruses that display HIV-1 envelope glycoprotein is enhanced when the glycoprotein is displayed on the surface of infectious virions.

Rockefeller University, New York City, and Bar-Ilan University, Ramat Gan, determined that, in populations positive for plasma HIV-1, rapid transient changes at the env gene locus take place during the emergence of resistance to protease-inhibitor drugs.

Viral Diseases. In research at the Laboratory of Viral Diseases (NIAID) and Tel Aviv University, study results indicate that human herpesvirus 7 (HHV-7) provides a *trans*-acting function that mediates reactivation of human herpesvirus 6 (HHV-6).

The University of California, San Francisco, the University of Oregon, Eugene, and Hadassah University Hospital, Jerusalem, reported that prion protein synthetic peptides induced cellular prion protein to acquire properties of the scrapie isoform.

Washington University School of Medicine, St. Louis, Missouri, and the Israel Institute for Biologic Research, Tel Aviv, found that neuroinvasiveness in Sindbis virus was associated with loci at both the position 8 and the E2 glycoprotein (Met 190) and that neuroinvasiveness could be induced in less lethal strains by substitutions at three loci (position 8, Met 190, and Lys 260).

Immunology. Investigators at the University of Tennessee, Memphis, and Hadassah University Hospital, Jerusalem, expressed an anti-DNA–associated Vh gene in immunized and autoimmune mice.

The University of California, Los Angeles, Boston University, Massachusetts, and the Weizmann Institute of Science, Rehovot, showed that cell-mediated cytotoxicity resulted from, but may not be critical for, primary allograft rejection.

Vector Biology. NIAID made a competitive foreign grant award to Hebrew University, Jerusalem, to study the role of plant diets of sand flies in the transmission of leishmaniasis in Israel.

Italy

University of Mali TMRC. La Sapienza University, Rome, is collaborating with this TMRC on field projects to identify populations of *Anopheles gambiae* mosquito vectors.

AIDS. Under the terms of the U.S.-Italy Science and Technology Health Sector Agreement, NIAID and Istituto Superiore di Sanità (ISS), Rome, encouraged Italian investigators to adopt AIDS Clinical Trial Unit protocols and to conduct complementary clinical trials in Italy. ISS is participating in two protocols of the AIDS Clinical Trials Group and is under consideration for participation in international studies of IL-2 by the Laboratory of Immunoregulation (NIAID).

Harvard Medical School, Boston, the International Center for Genetic Engineering and Biotechnology, Trieste, and the University of Padua have established that vectors of Moloney murine leukemia virus can be used as target cells susceptible to HIV-1 infection.

Tulane University, New Orleans, Louisiana, Harvard Medical School and Harvard School of Public Health, Boston, and the University of Padua showed that V1 and V2 variable loops of the gp120 envelope of HIV-1 play a part in protecting the virus from some subsets of neutralizing antibodies.

The University of California, San Diego, the Veterans Affairs San Diego Health Care System, the University of Miami, Florida, the University of Washington, Seattle, and the University of Milan characterized a molecular clone of HIV-2 that is infectious for *Macaca nemestrina* pigtail macaque monkeys.

San Raffaele Institute, Milan, is participating in a tricontinental study on the primary immune response to HIV infection.

The Population Council, New York City, and the University of Milan are trying to identify the mechanisms by which HIV-infected monocytes and macrophages transmit the virus in secretions of the genital tract.

NCI (NIH), the University of Kansas Medical Center, Kansas City, the University of Maryland, Baltimore, and ISS, Rome, found increased copy numbers for HHV-8 and increased viral gene expression in the peripheral blood mononuclear cells of patients with AIDS and Kaposi's sarcoma when the cells were cultured in the presence of inflammatory cytokines.

Bacterial Diseases. Although the NIAID clinical trials showing the safety and superior protection conferred by acellular pertussis vaccines compared with established whole-cell vaccines have been completed, NIAID continues to support ISS, Rome, for follow-up of these cohorts for long-term side effects and duration of protection. ISS and the University of Palermo have documented high titers of serum antibody and cell-mediated immunity to *Bordetella pertussis* in a cohort of Italian military school students with low immunization rates, indicating continuing transmission.

Mycotic Diseases. The University of Nevada School of Medicine, Reno, and the University of Perugia reported that encapsulation of *Cryptococcus neoformans* with glucuronoxylomannan inhibited the antigen-presenting capacity of monocytes. Researchers at Duke University, Durham, North Carolina, and the University of Ancona discovered that the immunosuppressant FK506 and a nonimmunosuppressant analogue, L-685,818, are toxic to *C. neoformans* through inhibition of a common target protein.

Viral Diseases. In studies at St. Jude Children's Research Hospital and the University of Tennessee, Memphis, and ISS, Rome, findings indicate that phosphorylation has a role in the nucleocytoplasmic transport of influenza virus nucleoprotein.

Immunology. Boston University School of Medicine, Massachusetts, and San Raffaele Scientific Institute, Milan, are investigating the secretion of soluble pre–B-cell receptors by pre-B cells.

The National Research Council, Rome, is a member of the NIAID-supported international study on HLA and mite-induced asthma. Johns Hopkins University, Baltimore, and the University of Milan have documented immunologic cross-reactivity among cereal grains and grasses in children with food hypersensitivity.

The University of California, San Francisco, Stanford University School of Medicine, California, and the European Institute of Oncology, Milan, discovered that a transgene for the retinoic acid receptor alpha of promyelocytic leukemia cells initiates development of acute promyelocytic leukemia in mice.

Japan

AIDS. The Laboratory of Immunology (NIAID), Yamaguchi University School of Medicine, and Nippon Medical School, Tokyo, are studying the reciprocal cytotoxic T-lymphocyte cross-reactivity interactions between two major epitopes within HIV-1 gp160.

In research at Thomas Jefferson University, Temple University School of Medicine, and St. Christopher's Hospital for Children, Philadelphia, Pennsylvania, and the Ajinomoto Company, Tokyo, findings suggest B-cell–mediated activation of V-delta-1 T lymphocytes during progression of HIV infection. Rockefeller University, New York City, and Kyoto University showed that nuclear factor kappa-beta and Sp1 transcription factors are coexpressed in dendritic cell–T-cell syncytia induced by HIV-1.

The University of Florida, Gainesville, and Kitasato Institute, Tokyo, used administration of maternal antiviral antibodies (passive antibodies) to protect neonatal kittens against infection with feline immunodeficiency virus.

The University of California, Los Angeles, and Osaka University reported that IL-6 induced target cell resistance to HIV-specific cytotoxic lysis. The University of California, Los Angeles, is also collaborating with Osaka Medical School and supports the work of Fujirebio, Inc., Osaka, in a nested case–control study within the U.S. Multicenter AIDS Cohort Study. The substudy is examining the relationship between IL-6 and AIDS-associated Kaposi's sarcoma.

Bacterial Diseases. Nihon and Rakuno-Gakuen (Japan) collaborated with the University of California, Davis, and the California Department of Fish and Game in documenting the presence of *Bartonella* spp. in a variety of wildlife in California.

The University of Alabama, Birmingham, Stanford University, California, North Carolina State University, Raleigh, Nihon University, Matsudo, and Ibaraki University, Hitachi, found that mucosally administered cholera toxin induced only antigen-specific B-cell responses in germ-free mice.

In a study at the University of California, Los Angeles, the University of Southern California, Los Angeles, Brigham and Women's Hospital, Boston, Massachusetts, Albert Einstein College of Medicine, Bronx, New York, and Tokyo Women's Medical College, findings indicate that non–peptide-reactive gamma/delta T cells conferred effective cell-mediated immunity to intracellular mycobacterial antigens.

Scientists at Cornell Medical College, Manhasset, New York, Roche Institute for Molecular Biology, Nutley, New Jersey, and Oita Medical University discovered that CD14-deficient mice demonstrated resistance to endotoxin and reduced dissemination of gram-negative bacteria.

The University of Alabama, Birmingham, and Osaka University reported that orally administered *Salmonella* that expresses fragment C of tetanus toxoid elicited mucosal IgA responses but accelerated colitis in IL-10 knockout mice.

The University of Alabama, Birmingham, the University of Mississippi Medical Center, Jackson, and Osaka University reported that oral immunization with pneumococcal surface protein A elicited a protective humoral immunity against *Streptococcus pneumoniae* in mice.

Mycotic Diseases. Stanford University School of Medicine, California, Keio University School of Medicine, Tokyo, and Kazusa DNA Research Institute, Chiba, found that the GAL11 protein of yeast binds to the transcription factor IIE through GAL11 regions essential for its in vivo function.

Parasitic Diseases. Using IL-3–deficient mice, Harvard Medical School, Boston, and Miyazaki Medical College, Kiyotake, showed that IL-3 is not essential to the generation of mast cells or basophils but does contribute to increased numbers of tissue mast cells, enhanced basophil production, and immunity, in mice infected with the nematode *Strongyloides venezuelensis.*

University of Colorado School of Medicine, Denver, Yale University, New Haven, and Osaka University determined that CD40-to-CD40 ligand interaction is required for the elimination of *Cryptosporidium parvum* infection in mice.

The Laboratory of Parasitic Diseases (NIAID) and Ehime University School of Medicine have completed the sequencing of the primary structure of a novel *Plasmodium vivax* ookinete surface protein.

Viral Diseases. The University of Alabama and the Veterans Affairs Medical Center, Birmingham, and the University of Tokyo demonstrated that amplification of recombinant adenoviral transgene products occurs by inhibition of histone deacetylase.

St. Jude Children's Research Hospital, Memphis, Tennessee, Hokkaido University, Sapporo, Tottori University, and Shizuoka University reported that differences in linkages between sialic acid and galactose in chicken egg amnion and allantois affect the receptivity and variant selection of human influenza A virus receptor.

Georgia State University, Atlanta, the University of Texas Medical Branch, Galveston, St. Thomas' Hospital, London, England, and the National Institute of Infectious Diseases, Tokyo, completed a long-term (1961–1997) molecular analysis of the epidemiology of rubella virus across Europe, Japan, and North America. The analysis demonstrated minimal change in the antigen during the 35 years of observation.

Immunology. Georgetown University, Washington, D.C., and Mie University determined that the concentrations of elastase in patients who have cystic fibrosis and chronic fatigue syndrome with nonallergic rhinitis are similar to those in healthy subjects. This finding makes it unlikely that increased vascular permeability, glandular secretion, or neutrophil infiltration contribute to the nonallergic rhinitis in patients with chronic fatigue syndrome.

The National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado, and Osaka University are studying the differential effects of gene targeting and antibody treatment against CD23 in allergic airway hyperresponsiveness.

In studies at the University of California, Davis, the National Jewish Center for Immunology and Respiratory Medicine, Denver, and Osaka City University Medical School, findings suggest that lamina propria lymphocytes in patients with Crohn's disease are selectively stimulated by a limited number of conventional antigens and that this stimulation may be important in the pathogenesis of the disease.

Kenya

Case Western Reserve Program Project. For the past 5 years, NIAID has supported an unsolicited program project (P01) submitted by Case Western Reserve University, Cleveland, Ohio, to collaborate with the Ministry of Health, Kenya, and the Kenya Medical Research Institute, in research on filariasis, hydatidosis, malaria, and schistosomiasis.

Parasitology. This project has demonstrated that in Kenya, where filariasis, schistosomiasis, and geohelminth infections are common, B-cell sensitization to helminthic infections develops in utero in humans.

Echinococcosis. With CDC and the Jomo Kenyatta University of Agriculture and Technology, Nairobi, investigators in the project determined that oxfendazole is at least as effective and is easier to administer than albendazole in animals naturally infected with *Echinococcus granulosus*.

Filariasis. The project is studying maternal–neonatal immune responses in pregnant women infected with filariae.

Malaria. The project focuses on malaria morbidity and gene mapping of Kenyan strains of *Plasmodium falciparum*.

Schistosomiasis. In studies on schistosomiasis, researchers are determining the prevalence of illness attributable to *Schistosoma mansoni* and *Schistosoma haematobium* in Kenya. The project reported that targeted chemotherapy in schoolchildren, which was begun in Msambweni in 1983–1990 to control *S. haematobium,* has reduced intensity of infection and urinary tract morbidity but has not had a long-term effect on prevalence or on sequelae such as hydronephrosis.

University of Washington HIVNET. The investigators at this HIVNET have evidence from a limited number of patients that distinct but related HIV-1 populations are harbored in genital secretions and blood at the same time in the same individual. They found that, in HIV-1–positive Kenyan women infected with clade A, phylogenetic and phenetic evolution of the structure of envelope sequences was detectable over time in mucosal and plasma viral samples. These findings suggest a continual process of migration of one or a few infected cells into each compartment, followed by localized expansion and evolution of that population.

University of Washington STD Cooperative Research Center. During FY 98, NIAID competitively renewed the University of Washington STD Cooperative Research Center, which has an international component in Kenya. The Center is collaborating with the University of Manitoba, Winnipeg, the University of Nairobi, and Coast Provincial General Hospital, Mombasa, in several projects with a common theme of prevention of morbidity from reproductive tract infection in females.

STD prevention and control. The Center evaluated the impact of a program to reduce behavioral risk in a cohort of trucking company employees in Mombasa. Investigators found a significant decrease in sexual activity with high-risk partners but no change in condom use. The change in high-risk heterosexual behavior was associated with a decrease in gonorrhea, nongonococcal urethritis, and genital ulcer disease.

Chlamydia trachomatis. One objective of the Center is to determine the immune pathogenesis of *C. trachomatis.*

Neisseria gonorrhoeae. Scientists at the Center are studying the role of the Opa antigen in the pathogenesis of gonorrheal infection and disease.

AIDS. The University of Washington, Seattle, the University of Nairobi, and Coast Provincial General Hospital, Mombasa, are carrying out phylogenetic evaluation of Kenyan HIV-1 isolates.

Kenya Medical Research Institute participates in the International *Mycobacterium avium* Complex Study Group. Recent activities included studies (1) on the epidemiology of disseminated *Mycobacterium avium-intracellulare* in AIDS and (2) on the risks and benefits of childhood BCG immunization of HIV-positive adults.

Parasitic Diseases. Kenya Medical Research Institute and the University of New Mexico, Albuquerque, are using internal described spacer sequences of genes and DNA assays to detect randomly amplified polymorphisms, in research on the interspecific and population genetic variation in *Schistosoma haematobium* and *Schistosoma bovis* in Kenya. In FY 98, NIAID made a new award to Case Western Reserve University, Cleveland, and the Ministry of Health, Kenya, to determine the genetic differences of patients infected with schistosomiasis who develop fibrosis in Kenya, where the prevalence of fibrosis is low, compared with patients in Egypt, where this complication is common.

Korea

Bacterial Diseases. The University of Idaho, Moscow, Washington State University, Pullman, and Seoul National University are investigating the ways in which staphylococcal enterotoxin C activates subpopulations of bovine lymphocytes.

Viral Diseases. In research at the University of Virginia, Charlottesville, the University of Science and Technology, Pohang, and Hallym University, Chuncheon, findings indicate that, although HCV core from two different genotypes has an oncogenic potential, it is not sufficient to transform primary fibroblasts from rat embryo in cooperation with the H-*ras* oncogene.

Immunology. Indiana University School of Medicine, Indianapolis, and Seoul National University found that a 30-kilodalton glycoprotein (4-1BB) is expressed on activated CD45RA(hi)RO(hi) transitional T cells in humans. In a recent study, these scientists worked with scientists from the Laboratory of Host Defenses (NIAID) to perform molecular cloning of leukotactin-1, a novel human beta-chemokine that is a potent chemoattractant for neutrophils, monocytes, and lymphocytes and an agonist at cysteine-to-cysteine chemokine receptors 1 and 3.

Lebanon

Immunology. In a study at Harvard Medical School, Boston, and American University of Beirut, findings indicate the existence of lipocortin-dependent and lipocortin-independent pathways by which glucocorticoids mediate their antiproliferative effects.

Madagascar

Parasitic Diseases. Case Western Reserve University, Cleveland, and Institut Pasteur, Antananarivo, are collaborating with groups in Europe to characterize SALSA, a novel *Plasmodium falciparum* sporozoite and liver stage antigen that defines major B-cell, helper T-cell, and cytotoxic T-cell epitopes.

Malawi

Johns Hopkins HIVNET. This HIVNET supports collaboration between Johns Hopkins University, Baltimore, and the Malawi College of Medicine, Blantyre, to carry out clinical trials of HIV/AIDS prevention.

Condom use. In prospective follow-up of Malawian women, reported condom use was substantially higher than in cross-sectional surveys, decreased rapidly over time regardless of HIV status, and was not associated with the incidence of new STDs. The findings suggest that this cohort of urban women overreported condom use, underreported sexual activity, or both.

Vaginal agents. The HIVNET administered a questionnaire on use of traditional vaginal drying agents and medicines and screened for HIV and STDs in 6,603 consenting women. These agents were used more frequently (34%) for self-treatment of vaginal discharge and itching than for vaginal tightening (14%). A higher proportion of HIV-positive women (17% vs. 14%) reported use of vaginal agents for self-treatment, but no difference was found in HIV status among women who used them for vaginal tightening.

Vitamin A. From the newborn cohort, the HIVNET has determined that children born to HIV-positive women who are deficient in vitamin A during pregnancy are significantly more likely to have growth failure.

AIDS. NIAID made a new grant award to Johns Hopkins University, Baltimore, and the University of Malawi College of Medicine, Blantyre, to evaluate adjunct vitamin A therapy for HIV/AIDS and tuberculosis.

Parasitic Diseases. Michigan State University and Kamuzu Central Hospital are conducting joint studies on cerebral malaria in children. The overall objective of the research is to advance understanding of the pathogenetic mechanisms involved in cerebral malaria, to generate new scientific approaches to treatment and prevention. The following hypotheses are being examined:

1. Cerebral malaria is caused by sequestration of parasitized red blood cells in the brain.
2. Increased intracranial pressure contributes to death.
3. Endothelial receptors for parasitized red blood cells are upregulated in patients dying of malaria compared with patients who have uncomplicated malaria and die of other causes. Intracerebral production of TNF-α and nitric oxide is enhanced in fatal cases.
4. Primary pathology of fatal pediatric malaria is within the central nervous system.

The investigators are working with investigators at the Liverpool School of Tropical Medicine, England, to determine the metabolic correlates of the severity and outcome of cerebral malaria.

Michigan State University, CDC, and the University of Malawi are looking at in-hospital mortality and morbidity associated with malaria-related anemia.

Malaysia

Parasitic Diseases. Smith College, Northampton, Massachusetts, and the University of Malaysia, Kelantan and Kuala Lumpur, have used PCR-ELISA for the detection of *Brugia malayi* infection. Findings show that the technique was specific and sensitive and detected more infections and that the test results were more reproducible than those from Southern blot hybridization.

Mali

University of Mali TMRC. This TMRC is supported by a direct award to the University of Mali, Bamako, but it involves collaboration with the Laboratory of Parasitic Diseases (NIAID), Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, the University of Maryland Medical Center, Baltimore, and other research groups.

Clinical manifestations. The TMRC reported that malarial parasitemia exceeding 5,000/mL was the threshold for clinical symptoms in semi-immune populations in Mali.

Preliminary data obtained with the Nutrition and Food Scientific and Technical Institute, Paris, suggests that in Malian children, hemoglobin AC (Hgb AC) confers a protective effect against mild malaria (fever) and hyperparasitemia and that iron supplementation is more protective in children with Hgb AA than in those with Hgb AS.

Epidemiology. The TMRC is conducting an epidemiologic study of the incidence of *Plasmodium falciparum* in a village-based cohort. The researchers are comparing morphological and molecular methods of measurement. Another TMRC project also uses global information systems and remote sensing to assess the effect of irrigated rice cultivation on risk of malaria in Mali.

In one protocol, researchers are examining the seasonal changes in gametocyte prevalence and density in human populations, as well as seasonal variation in gametocyte infectivity for mosquitoes.

Immunology. The TMRC is also examining seasonal changes in the immune activity that blocks transmission of the parasite or in natural antibodies to the pfs25 antigen of *P. falciparum.*

Clinical trials. This TMRC is carrying out a nested case–control study of the management of severe cerebral malaria. In one protocol, researchers are evaluating the use of four aminoquinolones in the treatment of falciparum malaria in Mali.

The scientists detected differences in gametocyte infectivity by direct mosquito feeds in an area of seasonal malaria transmission, compared with rates observed in laboratory-based feedings. This observation suggests use of caution in interpreting results of phase I laboratory-based studies as a surrogate for evaluation of the efficacy of vaccines against gametocyte malaria.

Vector biology. Preliminary results of joint research at Tulane University and the TMRC suggest that genetic recombination occurs during the meiotic reduction division in experimentally infected laboratory-reared progeny of *Anopheles gambiae*. The University of California, Los Angeles, La Sapienza University, Rome, and the TMRC used genetic marking and release and recapture to study the chronological variation of *A. gambiae* vectors in Banambani. The researchers documented substantial annual differences in the relative frequency of *A. gambiae sensu latu* (2.50%) and *Anopheles arabiensis* (10.77%), in the relative mean population size, but not in dispersal, which was usually less than 2 km.

Parasitic Diseases. The TMRC is investigating protective immunity in human filariasis. In addition, during FY 98, NIAID funded a new research grant to New York University, New York City, to work with the TMRC on the genetics of *A. gambiae* susceptibility to *Plasmodium parasites.*

Mexico

University ofTexas Medical Branch/Galveston Emerging Virus Center. This Center is collaborating with the National Institute of Forestry and Agricultural Research and the National Center for Microbiology Disciplines, Cuajambala, in the investigation of two recent outbreaks of Venezuelan equine encephalitis in Oaxaca and Chiapas. The scientists are working to determine the potential for reemergence of this disease elsewhere in Mexico and in North America.

Stanford University ICIDR. The ICIDR is conducting studies on the molecular epidemiology and the transmission of paucibacillary tuberculosis in Mexico.

AIDS. In research at the University of California, Los Angeles, and the Autonomous University of San Luis Potosi, findings indicate the existence of a self-reinforcing mechanism that affects TNF-α production, generalized immune activation, and HIV-RNA plasma levels.

Bacterial Diseases. Mycoplasma fermentans has been suggested as a possible cause of rheumatoid arthritis in humans. Scientists at the University of Alabama, Birmingham, the Medical Institute of Social Security, Mexico City, the National Polytechnical Institute, Mexico City, and the University of Puebla reported that, after intratracheal inoculation, *M. fermentans* was pathogenic to the intestinal tract of hamsters and the knee joints of rabbits.

Parasitic Diseases. Washington University, St. Louis, Missouri, and the National Polytechnical Institute, Mexico City, have identified B-cell epitopes in the serine-rich *Entamoeba histolytica* protein.

Viral Diseases. The National Institute of Public Health, Cuernavaca, is involved in an NIAID-supported multicenter study of the origin of highly pathogenic strains of dengue virus type 2 in the Americas.

Stanford University School of Medicine, California, the National Institute of Epidemiological Diagnosis and Reference, Mexico City, and the San Cristobal Department of Health, Chiapas, found that interference by Sabin type 2 oral poliomyelitis vaccine decreased the immunogenicity of Sabin type 3 poliomyelitis vaccine, after administration of trivalent oral polio vaccine to rural Mayan children.

The Netherlands

AIDS. The Municipal Health Services, Amsterdam, is participating in the Tricontinental AIDS Cohort Study. In addition, the Slotervaart Hospital, Amsterdam, is collaborating in a multicenter, international clinical trial of a new reverse transcriptase inhibitor, which is administered alone or in combination with AZT in HIV-positive patients. The University of Minnesota, Minneapolis, Abbott Laboratories (United States), Glaxo Wellcome Research and Development, Greenford, England, Municipal Health Services, and Slotervaart Hospital documented decreased levels of HIV-1 RNA in lymphoid tissue and peripheral blood during combination therapy with ritonavir, AZT, and β-1,2',3'-dideoxycytidine.

Bacterial Diseases. The National Jewish Center for Immunology and Respiratory Medicine and the University of Colorado Health Sciences Center, Denver, and Erasmus University, Rotterdam, reported that complement receptor type 3 mediated phagocytosis and killing of *Listeria monocytogenes* by a macrophage precursor hybrid that was stimulated by TNF-α and IFN-γ.

Mycotic Diseases. Georgia State University, Athens, Utrecht University Hospital, and Utrecht University Hospital for Children and Youth determined that the mannoproteins of *Cryptococcus neoformans* induced proliferative responses in human peripheral blood mononuclear cells and enhanced HIV-1 replication.

Viral Diseases. Yale University School of Medicine, New Haven, and Organon Teknika, Boxtel, are studying the protein components of the capsid antigen complex of Epstein-Barr virus and their relationship with ZAP21 protein.

Immunology. Boston University, Massachusetts, and Utrecht University determined that IL-16 is important for IgE synthesis and airway hyperresponsiveness in a mouse model for allergic asthma.

New Zealand

Immunology. Johns Hopkins Hospital, Baltimore, Children's Hospital of Philadelphia, Pennsylvania, the University of Washington and the Immunex Corporation, Seattle, and the University of Auckland found that, in addition to severely depressed antibody responses, patients with X-linked hyper-IgM syndrome have measurable T-cell defects, which may explain their susceptibility to opportunistic pathogens such as *Pneumocystis carinii.*

Norway

Immunology. Children's Hospital, Boston, Massachusetts, and the National Institute of Public Health, Oslo, have developed a mouse hybridoma "back pack" model, which may be a valid predictor of protection provided by natural mucosal immunization in vivo.

Pakistan

Bacterial Diseases. Colorado State University, Fort Collins, groups in England, and Aga Khan University and Marie Adelaide Leprosy Center, Karachi, tested 12 mycobacterial antigens for the induction of T_H1 cytokine responses in patients with tuberculoid leprosy. The scientists found that antigens containing cell wall, cytosolic, or membrane proteins produced the best induction of IFN-γ.

Panama

University of Texas Medical Branch/Galveston Emerging Virus Center. This Center and the U.S. Naval Medical Research Institute Detachment, Lima, Peru, used molecular epidemiology techniques to compare Panamanian isolates of Oropouche virus with those from other countries where the virus is endemic.

Papua New Guinea

Parasitic Diseases. Case Western Reserve University, Cleveland, Ohio, and the Papua New Guinea Institute for Medical Research, Goroka, are studying mother–infant immune interactions in filariasis and schistosomiasis.

Case Western Reserve University and the Papua New Guinea Institute for Medical Research performed genetic mapping for severe anemia secondary to malaria. The researchers have started studies to quantify the relative contribution of biologically plausible genes to malaria-associated anemia in the Abolem people, who live in an area where vivax malaria is endemic. More than 120 persons with this condition, including three sibling pairs, have been identified.

Peru

University of Texas Medical Branch/Galveston Emerging Virus Center. This Center and the U.S. Naval Medical Research Institute Detachment, Lima, conducted studies on the molecular epidemiology of Oropouche virus isolates from Peru and other countries where the virus is endemic.

Johns Hopkins ICIDR. During FY 98, NIAID and the National Institute of General Medical Sciences cosponsored a minority scientist from the Harvard School of Public Health, Boston, to carry out a research project at this ICIDR.

Emerging enteric pathogens. As a result of comparative studies with the ICDDR, Dacca, the ICIDR has gathered evidence that cholera and secretory diarrhea caused by enterotoxigenic *E. coli* may, at least in part, result from a reduction in gastric acid levels.

The HIVNET gathered evidence that *Clostridium difficile,* a common commensal bacterium in the bowel, is statistically more often associated with disease in HIV-positive patients with chronic diarrhea than in HIV-positive control subjects with no diarrhea.

Cysticercosis. CDC, the National Institute of Neurological Sciences, Lima, and the Beneficial Association Project in Information, Health, Medicine, and Agriculture, Lima, collaborate on the study of cysticercosis. The University of Michigan Medical School, Ann Arbor, two groups in England, the Beneficial Association Project in Information, Health, Medicine, and Agriculture, Lima, and the ICIDR found elevated concentrations of eotaxin and IL-5 in Peruvian patients with neurocysticercosis. The investigators are exploring whether these high concentrations trigger mechanisms for epilepsy, which occurs in patients with this disorder.

Baseline seroprevalence for *Taenia solium* was 14% in humans and 45%–70% in pigs. The copro-antigen test for *T. solium* eggs in stool was more sensitive than direct stool examination.

The preparative technique of polyacrylamide gel electrophoresis has allowed the isolation of most of the major antigens diagnostic for cysticercosis. The ICIDR discovered a new antigen band specific for tapeworm carriers, which is being evaluated. In addition, a new electrochemoluminescence assay is being developed.

Viral Diseases. Yale University School of Medicine, New Haven, the University of Michigan, Ann Arbor, and the U.S. Naval Medical Research Institute Detachment, Lima, have conducted studies on the epidemiology of transmission of endemic Oropouche virus in the upper Amazon in Peru. The results suggest that the virus has been endemic for many decades and that the human population is at considerable risk of infection.

Philippines

Research Institute for Tropical Medicine/Manila TMRC. The U.S. Naval Medical Research Unit, Jakarta, ALYKA, Puerto Princesa City, and the TMRC conducted a survey for chloroquine-resistant malaria in Palawan. The researchers found that, although all *Plasmodium vivax* strains responded to chemotherapeutic doses, there may be breakthroughs to chemoprophylactic doses. The frequency of *Plasmodium falciparum* resistance to standard therapy is at least 23%, but the level of resistance is low (R-1).

AIDS. The University of Washington, Seattle, and the Research Institute for Tropical Medicine, Manila, demonstrated the presence of multiple genetic subtypes of HIV-1 in the Philippines, extending the geographic range of previously reported genotypes in south and Southeast Asia.

Poland

Immunology. Yale University School of Medicine, New Haven, the University of Connecticut, Storrs, and Jagiellonian University, Kraków, reported that recombinant soluble T-cell receptors protected T cells from immune suppression. In research at Yale and Jagiellonian University, gamma/delta T cells from mice deficient in tolerized alpha/beta T-cell receptor inhibited contact sensitivity effector cells in vivo and their IFN-γ production in vitro. The investigators also showed that nonimmune cells sensitized with monoclonal IgE antibodies mediated adoptive cell transfer of contact sensitivity.

Portugal

Immunology. The Institute of Immunology, Lisbon, is a member of the multisite collaborative study on the association between HLSA genes and mite-sensitive asthma.

Romania

Bacterial Diseases. Scripps Research Institute, La Jolla, California, and the Institute of Biochemistry, Romanian Academy, Bucharest, reported that lactoferrin inhibited interaction of *E. coli* endotoxin with CD14+ T cells, by competition with the organism's lipopolysaccharide-binding protein.

Immunology. The University of Pittsburgh Cancer Institute, Pennsylvania, and the Center of Immunology, Bucharest, identified novel Fc-gamma-RIIc isoforms that are expressed by human natural killer T lymphocytes.

Russia

AIDS. NCI (NIH), Johns Hopkins School of Hygiene, Baltimore, and the Biomedical Center for AIDS, Cancer, and Related Problems, St. Petersburg, demonstrated that HIV-1 strains circulating in the blood of intravenous drug users and prostitutes in St. Petersburg have broad genetic diversity. This finding suggests multiple sources of introduction from different geographic sites.

The University of Alabama, Birmingham, the University of South Florida College of Medicine, Tampa, the University of Pennsylvania, Philadelphia, and the Institute of Viral Preparations, Russian Academy of Medical Sciences, Moscow, found that inoculation with HIV-2 DNA plasmids induced cross-reactive anti–HIV-2 and anti-SIV (macaque) immune responses in mice.

Bacterial Diseases. Rockefeller University, New York City, the Institute of Biochemistry and Physiology of Microorganisms, Moscow, and the Institute of Theoretical and Experimental Biophysics, Moscow region, reported that *Streptococcus pneumoniae* grown in the presence of clavulanic acid developed abnormal physiological properties and altered cell wall composition.

Viral Diseases. The University of California, Irvine, the Institute of Poliomyelitis and Viral Encephalitides, Moscow, and Moscow State University are studying how hepatitis A virus proteins 2C and 2BC induce rearrangement of the intracellular membrane.

St. Jude Children's Research Hospital, Memphis, Tennessee, has been collaborating with the Ivanovsky Institute of Virology, Moscow, on the molecular epidemiology of pandemic influenza.

Senegal

Harvard HIVNET. Study results from this HIVNET indicate that infection with both HIV-1 and HIV-2 is not a static condition. Levels of HIV-2 may decrease with disease progression and sequester in tissue reservoirs or, in many cases, HIV-1 may effectively outgrow HIV-2 in patients with both infections.

AIDS. Massachusetts General Hospital, Boston, and the University of Dakar have a new NIAID grant to study cytotoxic T-lymphocyte responses in infection with non–B clade HIV-1.

During FY 98, NIAID made a new grant award to the Harvard School of Public Health, Boston, and the University of Dakar to study HIV-2 as a model of primary HIV infection.

The University of Alabama, Birmingham, and the University of Washington, Seattle, are collaborating with the University of Dakar to perform an epidemiologic study of HIV-1 and HIV-2 in the cervix and vagina of Senegalese women infected with one or both of these retroviruses.

With the Institute of Pathology and Applied Cytology, Paris, the Institute of Social Hygiene, Dakar, and the University of Dakar, the University of Washington reported that both HIV-1 and HIV-2 are associated with human papillomavirus infection and that HIV-2 is also associated with squamous intraepithelial lesions of the cervix.

Singapore

Immunology. The University of Virginia, Charlottesville, and National University of Singapore determined that *Blomia tropicalis* allergen, an important cause of asthma in the tropics, is widely prevalent in house dust in Singapore. Subsequently, the researchers concluded that the allergen is highly immunogenic in Singapore and that it has little cross-reactivity with the recombinant antigen (Der p 5) of the North American mite D (*Pteronyssus*).

Slovakia

AIDS. The Picower Institute for Medical Research and North Shore University Hospital, Manhasset, New York, and the Slovak Academy of Sciences, Bratislava, showed that activation of the p38 mitogen-activated protein kinase cascade is critical for HIV-1 replication in primary lymphocytes and that blocking it may be a novel approach to treatment of HIV-1 infection. These scientists, with scientists at the State University of New York, Stony Brook, also found that cell proliferation is not required for productive HIV-1 infection of macrophages.

South Africa

University of Minnesota ICIDR. Historically, South Africa has been the site of particularly severe and invasive amebiasis. This ICIDR supports collaboration between the University of Minnesota and the Medical Research Council, Durban, to determine whether natural immunity develops after invasive amebiasis and asymptomatic intestinal infection. Hypotheses being investigated include the following:

- Cure of invasive amebiasis is followed by protective immunity against both invasive and asymptomatic infection with *Entamoeba histolytica*.
- Elimination of asymptomatic pathogenic and nonpathogenic *E. histolytica* is followed by long-lasting immunity to reinfection.
- Immunity to invasive amebiasis is dependent on sustained antigen-specific, cell-mediated immune responses, and immunity to intestinal infection requires a similarly specific IgA response.

The ICIDR is collaborating with El Hussain University Hospital, Cairo, Egypt, to elucidate the serum IgM antibody response to the galactose-inhibiting adherence lectin of *E. histolytica*. These researchers are also collaborating on a prospective study to detect *E. histolytica* and *E. dispar* after cure of amebic liver abscesses.

AIDS. The University of Alabama, Birmingham, New York University, New York City, and the University of the Free State, Bloemfontein, are participating in a multicountry study to characterize and titrate stock for challenge with an HIV-1 subtype E from chimpanzees. NCI (NIH), the University of Alabama, Birmingham, New York University Medical Center, New York City, Virogenetics Corporation, Troy, New York, and the University of the Free State, Bloemfontein, reported that immunization of chimpanzees with a recombinant canarypox HIV-1 virus did not confer protection to challenge with a heterologous cell-free HIV-1 strain.

Spain

AIDS. NCI (NIH), the University of Pennsylvania, Philadelphia, and the Autonomous University, Madrid, are studying the influence of the CCR2-V641 polymorphism on HIV-1 coreceptor activity and on the function of chemokine receptors.

San Pablo Hospital, Madrid, is a member of the multicenter group evaluating the safety, dosage, and antiviral effect of 1592U89, a new reverse transcriptase inhibitor. This agent is being administered alone or in combination with AZT to HIV-positive patients. The Provincial Hospital Clinic, Barcelona, is participating in an AIDS Clinical Trials Group study to determine which HIV-positive patients with a rash from pyrimethamine are at increased risk of developing toxoplasmic encephalitis.

Bacterial Diseases. The Uniformed Services University of the Health Sciences, Bethesda, Maryland, the University of Washington, Seattle, and the Autonomous University, Barcelona, found that *E. coli* strains producing prostatitis had neurovirulence profiles similar to those of strains from women with acute uncomplicated pyelonephritis.

Rockefeller University, NewYork City, determined that 50% of invasive isolates of pneumococci in Spain were resistant to penicillin.

Mycotic Diseases. Texas Tech University Health Sciences Center, Lubbock, and the University of Valencia identified ubiquitin-like epitopes associated with *Candida albicans.*

Immunology. La Jolla Cancer Research Foundation, California, Indiana University School of Medicine, Indianapolis, and the Autonomous University, Barcelona, determined that PU-1, a tissue-specific transcription factor, is involved in macrophage proliferation.

The University of Madrid is a member of the NIAID-funded international study of HLA genes and susceptibility to mite-induced asthma.

Sudan

Parasitic Diseases. The University of Alabama, Birmingham, the University of Khartoum, and Bilharzia Research Unit, Khartoum, conducted a field study showing that the specific mortality for schistosomiasis in the study village was 71 per 100,000.

Sweden

AIDS. The Dana-Farber Cancer Institute, Boston, Massachusetts, and the Biomedical Center, Uppsala, are working to elucidate the ultrastructure of HIV-1 genomic RNA. The scientists discovered a putative α-helical structure that overlaps the capsid-p2 boundary in the precursor to the gag protein in HIV-1. This precursor is critical for assembly of viral particles.

The University of California, San Francisco, the University of South Florida, Tampa, the University of Pennsylvania School of Medicine, Philadelphia, and the Karolinska Institute, Stockholm, developed a monoclonal antibody against HIV-1 gp41. This monoclonal antibody has demonstrated neutralizing activity against a variety of HIV-1 laboratory isolates.

The University of Massachusetts Medical School, Worcester, Duke University Medical Center, Durham, North Carolina, St. Jude Children's Research Hospital, Memphis, Tennessee, and the Karolinska Institute, Stockholm, are using immunization with DNA and boosting of immunization with recombinant vaccinia virus to screen HIV-1 env glycoproteins for the ability to raise neutralizing antibody.

Bacterial Diseases. The University of California, Los Angeles, West Los Angeles Veterans Affairs Medical Center, Memorial Sloan-Kettering Cancer Center, New York City, New York, Texas A&M University, College Station, and the University of Umeå purified and characterized a 66-kilodalton protein (Oms66) in the outer membrane of *Borrelia burgdorferi,* which functions as a porin. Examining a neurotropic strain of *Borrelia turicatae,* the University of California, Irvine, the University of Texas Health Sciences Center, San Antonio, and the University of Umeå determined that the function of the Vsp-OspC family of proteins of *Borrelia* could contribute to the differential localization in organs, including the brain, during infection.

The Laboratory of Immunoregulation (NIAID), Johns Hopkins School of Medicine, Baltimore, and the University of Umeå determined that a new enzyme time-release–touchdown PCR is 90% sensitive, 93.2% specific, and superior to existing tests for the diagnosis of pulmonary *Chlamydia trachomatis.*

Ohio State University, Columbus, the University of Texas Southwestern Medical Branch, Dallas, and the University of Göteborg identified a diffusible cytotoxin of *Haemophilus ducreyi* that may be responsible for the development or persistence of the ulcerative lesions seen in chancroid.

Parasitic Diseases. The Laboratory of Parasitic Diseases (NIAID), NCI (NIH), and the University of Stockholm reported that T-cell–derived IL-3 induced the production of IL-4 by non-B, non-T cells, which in turn amplified the T_H2-cytokine response to a nonparasitic antigen in mice infected with *Schistosoma mansoni.*

Viral Diseases. Vanderbilt University, Nashville, Tennessee, the University of California, Berkeley, the University of Stockholm, and the University of Uppsala have identified a novel mechanism of virus-to-virus interactions that involves the inhibition of DNA synthesis of phage T4 by the bacteriophage P2 tin protein.

The University of Alabama, Birmingham, is carrying out a phase III, double-blind, placebo-controlled trial of long-term therapy with valacyclovir in herpes encephalitis.

Yale University School of Medicine, New Haven, and the Karolinska Institute, Huddinge, found that infection with Semliki Forest virus evoked several independent mechanisms for blocking the entry of and for uncoating superinfecting viruses.

Immunology. The Medical College of Virginia, Richmond, and the Karolinska Institute, Stockholm, demonstrated that stimulation with lipopolysaccharide plus IL-4 or ligation of CD40 can induce dramatic morphological changes in murine B cells, which correlates with in vitro induction of strong cell adhesion.

Switzerland

Scripps Research Institute Hepatitis C Center. With University Hospital, Bern, this Center found that HCV induces specific cytotoxic T cells that recognize cytochrome P-450 sequences of the virus.

AIDS. The University of Geneva is part of an international consortium studying the primary immune response after acute HIV infection.

Stanford University, California, Roche Products (United Kingdom), and Hoffmann-La Roche, Basel, reported that exposure to higher drug levels of saquinavir for 24 weeks, even as monotherapy, resulted in a low level of multidrug resistance but, in the majority of patients, did not compromise options for future therapy with protease inhibitors.

Geneva University Hospital is part of a U.S.-Australia-Europe project to study the prevalence and clinical course of seroconversion in persons who had AZT-resistant HIV-1 in 1988–1994.

The University of North Carolina, Chapel Hill, the University of Zürich Hospital, and Canton Hospital, St. Gallen, reported that high levels of viremia with HHV-8 occur 1–2 years before the development of Kaposi's sarcoma; that persistent high viremia is not required for development of Kaposi's sarcoma; and that its development is a poor prognostic indicator.

Bacterial Diseases. Scripps Research Institute, La Jolla, California, North Shore University Hospital, Manhasset, New York, the University of Texas Southwestern Medical Center, Dallas, Bristol-Myers Squibb, Seattle, Washington, and the University of Geneva determined that lipoproteins of spirochetes such as *Treponema pallidum* and *Borrelia burgdorferi* activate monocytic cells via a CD14-dependent pathway different from that for lipopolysaccharide.

Parasitic Diseases. Biomedical Research Institute, Rockville, Maryland, Cornell University, Ithaca, New York, and the Basel Institute for Immunology reported that, in mice, IL-4 protected against severe intestinal inflammation during acute schistosomiasis.

Immunology. Johns Hopkins School of Medicine, Baltimore, and the University of Geneva reported that approximately one-third of children with moderate-to-severe atopic dermatitis also have IgE-mediated food allergy.

Tanzania

Bacterial Diseases. Tanzania is one of three countries participating in a community-based prospective evaluation of control of trachoma by single-dose annual administration of azithromycin compared with multiple doses of topical ophthalmic tetracycline ointment.

Thailand

Case Western Reserve ICIDR. This ICIDR provides funding to Case Western Reserve University, Cleveland, Ohio, to collaborate with Mahidol University, Bangkok, on the efficacy of adjuvant therapy with iron chelation in cerebral malaria.

Johns Hopkins HIVNET. This HIVNET supports collaborative research with Chiang Mai University, the Royal Thai Ministry of Health, and the Royal Thai Army Medical Corps.

Basic research. The HIVNET has studied full-length DNA sequences of the gene for subtype E HIV-1 envelope in persons from northern Thailand who had early seroconversion. The findings show that the diversity of gene sequences is increasing.

Behavioral change. The HIVNET conducted a prospective study in recruits to the Thai Army and Air Force, to elucidate the dynamics of risk behavior by measuring the frequency of self-reported sexual activity with female commercial sex workers. Despite an aggressive education program, the only significant reductions in visits to commercial sex workers were for recruits with a very high initial number of visits or for those who married.

With Mt. Sinai School of Medicine, the HIVNET found that hepatitis B vaccine, which requires three doses to immunize, was an incentive for commercial sex workers and male patients at STD clinics, but not for discharged recruits, to remain in prospective studies.

University of Massachusetts Dengue Program Project

Immunology. The investigators found that, after a second dengue infection with a different serotype in Thai children, cytotoxic T-lymphocyte responses, which were mainly cross-reactive to all dengue types, were directed against nonstructural proteins.

AIDS. The Laboratory of Immunoregulation (NIAID), New York University Medical Center and Rockefeller University, New York City, Cellgene Corporation, Warren, New Jersey, and Chiang Mai University conducted a pilot study of the relationship between thalidomide and *Mycobacterium tuberculosis* in HIV-positive Thai patients. Thalidomide administration was associated with weight gain and reduced levels of TNF-α and HIV viral load.

During FY 98, NIAID made a new grant award to Emory University, Atlanta, Georgia, to design and analyze the results of HIV vaccine trials in Thailand.

Parasitic Diseases. The University of California, San Francisco, and Mahidol University, Bangkok, studied the antifolate mutants of *Plasmodium falciparum* dihydrofolate reductase and proposed that drugs targeted to both the wild-type DHR and S108N mutant proteins in *P. falciparum* would have a low propensity for developing drug resistance and, hence, could be effective antimalarial agents.

Viral Diseases. The Armed Forces Research Institute of Medical Research, Bangkok, is involved in an NIAID-funded study on the origins of strains of dengue virus type 2 that are associated with increased pathogenicity in the Americas.

Trinidad and Tobago

University of Texas Medical Branch/Galveston Emerging Virus Center. Trinidad and Tobago is participating in the Center's multicountry study of the molecular epidemiology of Oropouche virus.

AIDS. Duke University, Durham, North Carolina, and the University of the West Indies, Port of Spain, have embarked on a comprehensive analysis of events that occur in primary infection with HIV-1 in an area of high transmission in Trinidad and Tobago. The program project (P01) will examine both cellular and cytotoxic reactions, as well as neutralizing antibodies that are present after acute infection.

Bacterial Diseases. The University of the West Indies, Port of Spain, participates in the NIAID-supported International *Mycobacterium avium* Study Group, which has investigated the epidemiology of disseminated *Mycobacterium avium-intracellulare* in diverse settings and has conducted a multicountry study of the risks and benefits of administration of BCG vaccine to patients with AIDS.

Turkey

Parasitic Diseases. Chicago Medical School, Illinois, Ege University, Izmir, and Diyarbakir University used the rK39 ELISA for the serodiagnosis and epidemiology of visceral leishmaniasis in Turkey. In addition to the expected documentation of canine and infantile visceral leishmaniasis, the results also point to the possible presence of (a) additional types of the disease in western Turkey and (b) a cutaneous–visceral type in the southeastern Turkey.

Immunology. The University of Virginia, Charlottesville, and the University of Ankara developed a recombinant ELISA to measure environmental levels of tropical plant allergens. The researchers also identified IgE antibodies specific for fungal allergen in Turkish and U.S. patients with atopic dermatitis.

Uganda

Columbia-Johns Hopkins Rakai Program Project. This program project (P01) involves Columbia University, New York City, Johns Hopkins University, Baltimore, Makere University, Kampala, and the Uganda Virus Research Institute, Entebbe, in a large village-based project to measure the reduction in prevalence of HIV after treatment for STDs. Other institutions collaborating in the research are the Laboratory of Immunoregulation (NIAID) and the University of Pittsburgh, Pennsylvania.

During FY 98, the investigators reported that, in couples discordant for HIV status in this rural setting, men were the predominant source of new infections. Risk factors and preventive behaviors varied with the gender of the infected partner, but seroconversion rates were similar for both genders.

Epidemiology. In Rakai, where the HIV epidemic is mature, HIV prevalence declined in the face of a stable and high incidence. The paradox is due to the fact that HIV-related mortality contributed most to the decline in prevalence. This finding indicates that prevalence is not a useful surrogate measurement of incidence as a means to evaluate the impact of prevention or treatment strategies in this setting.

Sexually transmitted diseases. In Rakai, HIV-1 infection is associated with abnormal morphology of vaginal flora and with bacterial vaginosis, particularly in younger women. This finding suggests that abnormal flora increase risk of contracting HIV.

AIDS. During FY 98, NIAID competitively renewed the program project (P01) in AIDS, at Case Western Reserve University, Cleveland. The project provides support to the Case Western HIVNET activities in Uganda.

Johns Hopkins School of Medicine, Baltimore, Abbott Laboratories, Chicago, Illinois, and Nakasero Blood Bank, Kampala, determined that, despite the sequence variation of HIV-1 in Uganda, commercial enzyme immunoassays based on HIV-1 clade B proteins detected all infections. In contrast, a peptide-based assay failed to detect three clade D infections.

NIAID supports the University of Minnesota, Twin Cities, to piggyback another study on a continuing clinical trial of pneumococcal vaccine in HIV-positive patients. The purpose of the new study is to determine whether this immunization is associated with more rapid HIV progression and, if so, to examine the factors involved.

Bacterial Diseases. During FY 98, NIAID made a new career award to a scientist at Case Western Reserve University, Cleveland, to study the role of T-cell apoptosis in the immunopathogenesis of tuberculosis. The award will build on the work of the Tuberculosis Prevention Research Center and HIVNET in Uganda.

United Kingdom

AIDS. In research at CDC, the University of Michigan Medical Center, Ann Arbor, and St. George's Medical School, London, England, findings suggest that surface adhesion molecules contribute to regulatory signaling for the control of HIV-1 replication, possibly through the liberation of cytokines that act locally.

The Aaron Diamond Research Center, New York City, New York, and the Institute of Molecular Medicine, Oxford, and Oxford University, England, determined that cytotoxic T cells have a significant role in controlling HIV infection and probably have a considerable cytopathic effect on the virus.

The University of Pittsburgh Medical Center, Pennsylvania, Emory University, Atlanta, Georgia, the Wellcome Foundation, Beckenham, England, and MediTech Media, Ltd., London, England, reported that mutations in HIV-1 reverse transcriptase and protease were associated with drug resistance.

During FY 98, NIAID made a new foreign grant award to the United Medical and Dental School, Guy's Hospital, London, England, to investigate chemokines and cytokines in mucosal SIV infection.

The National Institute for Biological Standards and Control, Potter's Bar, is involved with New York University in an international consortium to study the in vitro and in vivo infectivity of different clade B HIV-1 chimeric SIV and HIV in macaque monkeys.

An award to the University of London, England, supports development of an immunization strategy using SIV in nonhuman primates to stimulate three levels of rectal immunity that correspond to the three phases of HIV infection.

The London School of Hygiene and Tropical Medicine participates in a study of the NIAID AIDS Clinical Trials Group. In that study, patients receiving antiretroviral therapy who experienced a decrease in viral levels of HIV-1 RNA, an increased CD4+ lymphocyte count, or both had a delay in clinical disease progression.

The University of Cincinnati, Ohio, the Royal Free Hospital Medical School, London, England, and Glaxo Wellcome Research, Research Triangle Park, North Carolina, and Beckenham, England, used PCR technology to measure cytomegalovirus viremia and viruria in HIV-positive patients. Study results indicate that PCR provided prognostic information about cytomegalovirus disease in HIV-positive patients.

Bacterial Diseases. Colorado State University, Fort Collins, and SmithKline Beecham, Brockham Park, Surrey, England, are determining whether the mycobacterial cell envelope can serve as a target for novel drugs against tuberculosis.

Rockefeller University, New York City, and the University of Sussex, England, are studying genes for response to penicillin in antibiotic-resistant pneumococci.

Parasitic Diseases. NIAID made a new foreign award to the Royal Post-Graduate Medical School, London, England, for research on chemokines and inflammatory responses in cysticercosis.

New York University Medical Center, John Radcliffe Hospital, Oxford, England, and the Imperial College of Science, Technology, and Medicine, London, reported that thrombospondin-related anonymous protein is necessary for gliding motility and infectivity of *Plasmodium sporozoites*.

The Laboratory of Parasitic Diseases (NIAID), Palo Alto Medical Foundation and Stanford University School of Medicine, California, Washington University, St. Louis, Missouri, and Oxford University determined that partially protective vaccination is associated with the development of latency in a normally virulent strain of *Toxoplasma gondii*.

Viral Diseases. The Institute for Cancer Research, London, England, is part of a consortium examining the genetic variation of HHV-8 in individuals and among viruses from different geographic sites.

Utah State University, Logan, Gilead Sciences, Inc., Foster City, California, the University of Birmingham, England, and Pfizer Central Research, Sandwich Park, England, demonstrated that oral administration of a prodrug of the influenza virus neuraminidase inhibitor GS 4071 protected both mice and ferrets against infection.

Scripps Research Institute, La Jolla, California, and the University of Dundee, Scotland, determined that HBV transcription, particularly pregenomic RNA synthesis of HBV, is regulated by ligand-dependent receptors and that agonists and antagonists capable of regulating the activity of these nuclear receptors may permit modulation of HBV transcription and consequent replication.

NIAID is funding a foreign award to the Medical Research Council, United Kingdom, to study cytotoxic T-cell responses to measles in infants and children in the Gambia.

Immunology. The Trudeau Institute, Saranac Lake, New York, Genentech, Inc., San Francisco, California, and Oxford University are searching for a possible role for IFN-γ in the regulation of B-cell proliferation during an immune response.

Oxford University participates in an international study of the association between HLA genes and mite-sensitive asthma around the world. The University of Manchester, England, is part of another group that is conducting a multicenter study of the biological activity of recombinant group 5 antigens of mites.

Venezuela

University ofTexas Medical Branch/Galveston Emerging Viruses Center. With CDC and the National Institute of Hygiene and the Ministry of Health and Social Assistance, Caracas, the Center conducted epidemiologic and clinical studies of 165 patients with Venezuelan hemorrhagic fever, a newly emerging viral zoonosis caused by Guanarito virus. The disease peaked in the November 1997–January 1998 agricultural season in male agricultural workers and produced an overall fatality rate of 33.3%, despite hospitalization and vigorous supportive care.

Viral Diseases. The National Institute of Hygiene, Caracas, is participating in a multicenter NIAID-sponsored study of highly pathogenic dengue virus type 2 in the Americas.

Vietnam

AIDS. The University of Hawaii, Honolulu, the University of California, Los Angeles, and Hanoi Medical College identified HIV-1 subtype E in both commercial sex workers and injection drug users in southern Vietnam. The University of Hawaii, Honolulu, and the University of California, Los Angeles, are now collaborating with the National Institute of Hygiene and Epidemiology, Hanoi, to determine the sequence and phylogenetic analyses of HIV-1 clade E in commercial sex workers and injection drug users in Vietnam.

Zambia

University of Alabama/Birmingham HIVNET. Since November 1997, the HIVNET has provided support to the University of Alabama, Birmingham, to collaborate with the University of Zambia, Lusaka. The main focus of the HIVNET is on heterosexual transmission and the natural history of HIV/AIDS in Zambia.

Heterosexual transmission. In collaboration with Walter Reed Army Institute of Research, Washington, D.C., and the University of Nottingham, England, the HIVNET intensively studied the transmission and evolution of HIV-1 in a Zambian couple. Findings indicate that recombination of HIV-1 intersubtypes played a central role and may contribute substantially to the rapid emergence of HIV-1 variants when HIV-1 infections of mixed subtype occur.

Treatment. The HIVNET found that active promotion of voluntary HIV testing and counseling in couples is necessary to reduce HIV spread in areas of high prevalence such as Zambia. Rapid onsite HIV testing performed by HIVNET staff allows clients, in a single visit, to receive result-specific counseling along with quality control of a subset of samples at an outside laboratory.

AIDS. The multidisciplinary AIDS Center at the University of Alabama, Birmingham, has NIAID funding to support the HIVNET activities in Zambia.

Viral Diseases. Zambia University Teaching Hospital, Lusaka, participates in an international study of the diversity of HHV-8 in individual patients and in different geographic areas.

Zimbabwe

Stanford University HIVNET. NIAID support to Stanford University, California, to work with the University of Zimbabwe, Harare, began with a PAVE award in 1991 and is now supported by this HIVNET. The current HIVNET supports joint research activities with the University of Zimbabwe to define the mechanisms and pathogenesis of perinatal HIV transmission and to conduct longitudinal studies of HIV in heterosexual industrial workers.

Risk factors. Working together, Chiron, Emeryville, California, and the HIVNET found an association between HIV-1 infection and seropositivity for herpes simplex virus type 2 (HSV-2) in male factory workers. The results have raised the possibility of using HSV-2 suppression as a strategy to reduce HIV transmission and of using HSV-2 seroconversion as a surrogate end point for evaluation of interventions to prevent HIV.

Perinatal studies. In the HIVNET's perinatal research, the study population consists of a cohort of 350 pregnant HIV-positive women and their children who have had follow-up since 1991. The studies in Zimbabwe, predominantly on clade C, parallel virological and serological studies on clade B in Europe and the United States. Prolonged breast-feeding in Zimbabwe adds another dimension to these prospective studies.

Studies of factory workers. The HIVNET also has provided an opportunity for the University of Colorado Health Sciences Center, Denver, to study the epidemiology of HHV-8 and Kaposi's sarcoma in these populations. Preliminary results show higher prevalence of antibodies to HHV-8 in HIV-negative men with endemic Kaposi's sarcoma (40%) than in HIV-positive men (23%) or HIV-positive women (11%).

Taiwan

AIDS. The University of California, Los Angeles, and Chang Gung Children's Hospital, Linkou, determined that complement from healthy persons can enhance gp120-specific antibody-dependent cellular cytotoxicity and that fresh HIV-positive serum is more active than heat-inactivated serum. This finding suggests that certain heat-labile inhibitory factors are present in HIV-positive serum. With researchers at Immunex Corporation, Seattle, these researchers determined that IL-15 restores impaired activity of 7-day, lymphokine-activated killer cells in HIV-positive patients and, therefore, may be a candidate for immunomodulative therapy in HIV/AIDS.

Activities With International and Multinational Organizations

United Nations AIDS Agency

NIAID supports the United Nations AIDS (UNAIDS) Agency Network for HIV Isolation and Characterization through formal collaboration with more than a dozen NIAID-supported laboratories in the United States. Within this collaboration, NIAID is responsible for the analysis of viral isolates obtained from four UNAIDS sites, in Brazil, Rwanda, Thailand, and Uganda. The NIAID-funded contract at Los Alamos, New Mexico, supports the database for this activity.

The NIAID AIDS Research and Reference Reagent Program collaborates with WHO and the UNAIDS Agency in the acquisition, distribution, and storage of reagents for use by the international scientific community. HIVNET studies are often conducted in collaboration with UNAIDS. The DAIDS (NIAID) Associate Director for Vaccine and Prevention Research is a member of the UNAIDS Vaccine Advisory Committee.

NIAID collaborates with UNAIDS on prenatal, intrapartum, and postnatal strategies or combination of strategies to interrupt mother-to-infant transmission of HIV. NIAID has collaborated with WHO and UNAIDS in efforts to implement UNAIDS guidelines for the use of antiretroviral agents to prevent mother-to-infant transmission of HIV in resource-poor settings. The HIVNET Perinatal Working Group includes a UNAIDS representative.

United Nations Development Program

Harvard Medical School, Boston, Massachusetts, and the University of Padua, Italy, are collaborating with the United Nations Development Program's International Center for Genetic Engineering and Biotechnology, Trieste, Italy, on the truncation of HIV-1 envelope glycoprotein to permit efficient pseudotyping of Moloney murine leukemia virus particles and gene transfer into CD4+ T cells.

International Meetings

NIAID staff participated in the following meetings in FY 98:

- Participating agency meeting on Multilateral Initiative in Malaria, in London, England, on November 12, 1997;
- Indo-U.S. Vaccine Action Program, Commercial Colloquium on Rotaviral Diarrhea, in Bangalore, India, on December 1–3, 1997;
- U.S.-Japan Cooperative Medical Sciences Program (CMSP) joint panel meeting on Cholera and Related Diarrheal Diseases, in Clearwater Beach, Florida, on December 3–5, 1997;
- U.S.-Japan CMSP joint panel meeting on Acute Respiratory Infections, in Houston, Texas, on January 12–13, 1998;
- U.S.-Japan CMSP joint panel meeting on Hepatitis, in Monterey, California, on January 27–29, 1998;
- U.S.-Japan CMSP Joint Subcommittee on Program Review and Planning, in Kona, Hawaii, on February 12–13, 1998;
- NIAID Collaborative Antiviral Study Group Meeting, in Bethesda, Maryland, on February 17–20, 1998;
- Workshop on a Blueprint for TB Vaccine Development, in Rockville, Maryland, on March 5–6, 1998;
- U.S.-Japan CMSP workshop on Emerging and Reemerging Infectious Diseases, in Bali, Indonesia, in March 1998;
- U.S.-Japan CMSP joint panel meeting on AIDS, in Williamsburg, Virginia, on March 18–20, 1998;
- XXth Mycoses Study Group Meeting, in Bethesda, Maryland, on April 22–24, 1998;
- VIIth Annual International Centers for Tropical Disease Research Meeting, in Bethesda, Maryland, on May 4–6, 1998;
- U.S.-Georgia Workshop on Research Opportunities in AIDS and Other Emerging Infectious Diseases in the Caucasus, in Tbilisi, Georgia, on May 12–15, 1998;
- IInd U.S.-Russian Workshop on Research Opportunities in AIDS and Other Emerging Infectious Diseases in the Former Soviet Union, in St. Petersburg, Russia, on May 18–20, 1998;
- expert panel on Basic Immunology of Vaccines, in Bethesda, Maryland, on June 9, 1998;
- NIH workshop on Research Issues Related to the Eradication of Poliomyelitis, in Bethesda, Maryland, on June 10–11, 1998;
- Workshop on Molecular and Structural Approaches to Antiviral Drug Design, in Bethesda, Maryland, on June 24–25, 1998;
- Workshop on Application of the *Staphylococcus aureus* Genome Database, in Rockville, Maryland, on June 29–30, 1998;
- U.S.-Japan CMSP joint panel meeting on Tuberculosis and Leprosy, in Osaka, Japan, on July 8–10, 1998;
- Workshop on The Role of Genetic Factors in Infection and Immunity, in Tokyo, Japan, on July 13, 1998;
- U.S.-Japan CMSP joint meeting in Tokyo, Japan, on July 14–15, 1998;
- U.S.-Japan CMSP joint panel meeting on Parasitic Diseases, in Chiba, Japan, on August 25–27, 1998; and
- U.S.-Japan CMSP joint panel meeting on Viral Diseases, in Kyoto, Japan, on September 2–4, 1998.

VII.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

INTRODUCTION

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) conducts and supports basic and clinical research on many of the most debilitating diseases affecting the Nation's health, including the many forms of arthritis, osteoporosis, and other diseases of the musculoskeletal system and the skin. The normal structure and function of joints, muscles, bones, and skin are addressed as well. Basic research involves a wide variety of scientific disciplines, including immunology, genetics, molecular biology, structural biology, biochemistry, physiology, virology, and pharmacology. Clinical research, including epidemiologic studies and clinical trials, is conducted in the fields of rheumatology, orthopedics, bone endocrinology, sports medicine, and dermatology.

The Extramural Program of NIAMS supports research and research training at universities and medical centers through research grants and contracts. The four program branches deal with rheumatic diseases, muscle biology, musculoskeletal diseases, and skin diseases. The Intramural Research Program conducts research on the campus of the National Institutes of Health (NIH), Bethesda, Maryland. The Program consists of the Arthritis and Rheumatism Branch, the Bone and Connective Tissue Biology Branch, the Laboratory of Physical Biology, the Protein Expression Laboratory, the Laboratory of Skin Biology, and the Laboratory of Structural Biology Research.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

The Workshop on Stem Cell Therapy for Rheumatic and Autoimmune Diseases, which was organized by NIAMS with support from the Office of Rare Diseases, was held in Bethesda, Maryland, on September 11, 1998. The meeting brought together an international group of researchers to discuss the current status of research and the coordination, design, and reporting of clinical trials of stem cell therapy to treat advanced rheumatic and autoimmune diseases. Such trials have been designed in Australia, Canada, Europe, and the United States to assess the safety, methods, and effect of stem cell therapy, including autologous bone marrow transplantation and therapy using peripheral blood stem cells.

The Director, NIAMS, opened the meeting by acknowledging ongoing research and by stressing the need to share data and research opportunities. The workshop participants agreed on the need for further discussion of four topics: (1) broad principles for study design, (2) protocol design, (3) animal models and ancillary studies, and (4) the research community. They recommended the following actions:

- creation of systematic international mechanisms and registries for sharing data;
- development of international working groups to encourage communications and planning for research on stem cell therapy; and
- formation of international subcommittees designed to develop consensus on protocols for each of the major rheumatic and autoimmune diseases.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Activities With International and Multinational Organizations

International Council of Scientific Unions

The Scientific Director, NIAMS, participated in the Extraordinary General Assembly of the International Council of Scientific Unions as the representative of the International Union of Immunological Societies, in Vienna, Austria, in April 1998. He also served as a member of the council's Committee on Membership and Statutes and as a representative of the U.S. National Academy of Sciences.

Medical Planning Committee of the Canadian Arthritis Society

The Chief of the Clinical Investigations Section served as the official U.S. representative to the Medical Planning Committee of the Canadian Arthritis Society.

Extramural Programs

Skin Diseases Branch

An NIAMS grantee at the Medical College of Wisconsin, Milwaukee, continues to collaborate with and has a subcontract with investigators at the University of São Paulo, Brazil. This joint research team has focused on the blackfly species that are present in the areas of endemic pemphigus foliaceus (fogo selvagem) in Brazil as the likely trigger of autoimmune events in susceptible populations. They have compared the subspecies present in villages where there is high prevalence of disease with genetically similar subspecies in nearby villages where there is little disease present. The scientists discovered a wider variation in subspecies than had been suspected. They are now characterizing the antigens from these blackfly subspecies to determine which antigen or antigens are the likely environmental trigger(s) for the disease.

International Meetings

On January 17, 1998, the Director, NIAMS, was the Alfred Marchionini Lecturer, in Hamburg, Germany. The theme of his presentation was The Skin Immune System—Why Study It? The Director discussed the skin immune system with particular emphasis on clinical immunopathological correlations and on what current immunobiology teaches us about common skin diseases. He discussed some of the early events in contact hypersensitivity, as well as the most recent NIAMS studies on the use of DNA vaccination through the skin.

During the week of February 9, 1998, the Director, NIAMS, was invited to be a visiting professor at the St. John's Institute of Dermatology, London, England. The purpose of the visit was to meet with members of the faculty to discuss research and other topics and to give three lectures. These lectures were on The Impact of Molecular Biology on Dermatology, The Use of Skin for DNA Sensitization, and discussions on the setting of research priorities. On February 12–15, the Director was in Helsinki, Finland, to give an invited guest lecture as he became an Honorary Member of the Finnish Dermatological Society.

The Director, NIAMS, participated in joint meetings in Montaccatini Terme, Italy, in March 1998. He was invited to speak on Scientific Opportunities in Scleroderma Research, at the International Conference on Systemic Sclerosis, and to give the opening lecture, on Immunobiology of Skin, at the Renaissance of Dermatology International Meeting.

The Head of the Signal Transduction Group hosted the International Conference on Signal Transduction in Mast Cells and Basophils, at the NIH, Bethesda, Maryland, in March 1998. He was also an invited speaker at the National Institute of Medical Research, London, England, and at the Hospital Cochin, Paris, France, in September 1998.

The Chief of the Laboratory of Structural Biology Research presented a seminar at Institut Ebel de Biologie Structurale, Grenoble, France, on April 3, 1998.

On April 17–18, 1998, the Director of the Musculoskeletal Diseases Branch attended a meeting in Lund, Sweden, to discuss an initiative entitled The Bone and Joint Decade 2000–2010. The meeting was held to develop an action plan to focus attention on prevention and treatment in the field of musculoskeletal disorders and to stimulate research efforts. Participants included rheumatologists, orthopedic surgeons, bone endocrinologists, and trauma surgeons. The attendees were largely editors of the scientific and medical journals in the field and representatives of the major scientific and voluntary organizations, as well as the World Health Organization and the United Nations.

The Chief of the Connective Tissue Diseases Section attended a meeting of the Argentine Society of Rheumatology, in Buenos Aires, in April 1998, where he delivered several lectures. He also visited the University of Toronto, Ontario, in April 1998, and made presentations there.

The Chief of the Genetics Section was invited to give a lecture at the Institute of Molecular and Cellular Biology, Porto, Portugal, on April 30, 1998. He also gave an invited lecture at the Sheba Medical Center, Tel Hashomer, Israel, on May 4, 1998. On May 5–6, the Chief was invited to give two lectures at the 5th Congress of Clinical Molecular Genetics, at Ankara University, Turkey, where he also gave a Pediatrics Grand Rounds lecture at Hacettepe University, Ankara, on May 6.

The Chief of the Genetic Studies Section made a presentation at the International Investigational Dermatology 1998 Conference, in Cologne, Germany, in May. The Section Chief also made a presentation and chaired a scientific session at the Satellite Symposium on Inherited Skin Diseases, in Rome, Italy, in May 1998. A staff scientist in the Genetic Studies Section presented a poster at both meetings.

The Chief of the Craniofacial Development Section, Bone and Connective Tissue Biology Branch, participated in the Pierre Fauchard Academy Continuing Education Program, in London, England, on June 22, 1998. The Chief was an invited speaker at the 30th Anniversary European Research Group for Oral Biology Conference, in Interlaken, Switzerland, on August 20–23, 1998. He also gave a seminar entitled The Oral Cavity and Human Gene-Mediated Diagnostics and Therapy.

The Director, NIAMS, was invited to the Mexican Academy of Dermatology Meeting, in Mexico City, on July 24–25, 1998. He gave two lectures: The Skin Immune System and Advances in Science Related to Dermatology.

In July 1998, the Chief of the Inflammatory Joint Tissue Diseases Section and a staff scientist presented a seminar at the XIIth International Workshop on Alloantigenic Systems in the Rat, in Halifax, Nova Scotia. The Chief also presented a seminar at the 12th Annual Symposium on the Long-Term Effects of Estrogen Deprivation, in Los Cabos, Mexico, in July. In September 1998, he presented the keynote address at the 1st International Conference on the Neuroendocrine Immune Basis of the Rheumatic Diseases, in Genoa, Italy.

The NIAMS Director was invited to participate as a guest lecturer at the Kaposi Mór Dermatological Summer Seminars, entitled Masters of Dermatology, in Budapest, Hungary, on August 7–8, 1998. The title of the lecture was The Skin Immune System—Why Study It?

In September 1998, the Chief of the Chemical Immunology Section was a speaker at plenary sessions of the 11th Meeting of the Collegium Internationale Allergologicum, in Corfu, Greece, and of the 10th Meeting on Signal Transduction in Balaton Süd, Hungary.

Also in September, the Chief of the Clinical Investigations Section gave lectures at two plenary sessions at the XXIInd Uruguayan Congress on Rheumatology, in Piriapolis, Uruguay.

The NIAMS Director presented a plenary session on Immunobiology of the Skin, at the 5th Asian Dermatological Congress, in Beijing, China, on October 14–17, 1998.

The NIAMS Director was an invited lecturer at the VIIIth Meeting of the European Immunodermatology Society, in Rome, Italy, on November 19–21, 1998. His presentation addressed recent advances in understanding the mechanism underlying contact sensitivity.

The Chief of the Laboratory of Skin Biology was an invited participant in February 1998, at the meetings of the Korean Society for Investigative Dermatology, in Seoul and Taejon, Korea, and in May 1998 at the International Symposium on Keratinization and Its Disorders: A Molecular Perspective, in Kloster Walberberg, Germany; at the 3rd International Investigative Dermatology Meeting, in Cologne, Germany; and at the Satellite Symposium on Inherited Skin Diseases, in Rome, Italy. In February 1998, the Chief also gave seminars, lectures, or both at Samsung Medical School, Seoul; Chungnam National University, Taejon; and Korea University, Seoul.

A Guest Researcher from Japan, in the Craniofacial Development Section, presented his work at two meetings: the 37th American Society for Cell Biology Annual Meeting, in Washington, D.C., on December 17, 1997, and the 7th Annual Meeting of the Society of Hard Tissue Biology, in Tokyo, Japan, on March 16, 1998. The presentation was entitled BMP4 Induced Ectopic Cartilage Formation in the Mouse Embryonal Mandibular Process: BMP4 Mediates Msx2 and Sox9 Expression During Chondrogenesis.

Two fellows in the Clinical Investigations Section presented their work at the XVIIIth European Workshop for Rheumatology Research, in Athens, Greece, on March 12–15, 1998.

A Visiting Associate from Japan presented his work on BMP4 Induced Chondrogenesis by Upregulation of an Activator Sox9 and a Repressor Msx2, at the 27th Annual Meeting of the American Association for Dental Research, Minneapolis, Minnesota, on March 20, 1998.

Intramural Programs and Activities

Arthritis and Rheumatism Branch

Chemical Immunology Section

A Visiting Fellow from Japan was the first author on an important report that described a novel molecular mechanism by which low-affinity ligands can noncompetitively inhibit the action of high-affinity ligands in the immune system. The report received special comment in the journal *Science.*

Connective Tissue Diseases Section

The Connective Tissue Diseases Section continued an active collaboration on glycogen storage disease type II (acid maltase deficiency) with colleagues at the Hospital Debrousse, Lyon, France, and Erasmus University, Rotterdam, the Netherlands.

A Visiting Fellow from China continued working on the gene for acid α-glucosidase (acid maltase). Another Visiting Fellow, from India, continued working on the pathogenesis of myositis.

Genetics Section

The Genetics Section entered into joint research with a group in London, England, to identify the gene that causes familial Hibernian fever. The Section also continued active collaboration with a group in Israel to study the genetics of familial Mediterranean fever (FMF).

A Visiting Fellow from Armenia is studying mutations of the gene for FMF (MEFV) in patients with FMF in Armenia and the United States. Two Exchange Scientists from Israel worked in the Genetics Section to characterize mutations in patients with FMF. A Visiting Fellow from Korea is working to develop an FMF knockout mouse. An Exchange Scientist from Portugal is studying the genetics of familial amyloid polyneuropathy. Another Exchange Scientist, from Turkey, is studying the frequencies of FMF mutations in the Turkish population.

Inflammatory Joint Diseases Section

A Visiting Fellow from Bulgaria presented a report at the Endocrine Society Meeting in July 1997. He is also the first author of a report that was published in the *Journal of Immunology,* in September 1998: "Histamine, via H2 Receptors, Has Potent and Opposite Effects on Human Interleukin-12 and Interleukin-10 Production." In addition, the investigator is a coauthor of another journal article, "Hormonal Regulation of TNF-alpha, IL-12, and IL-10 Production by Activated Macrophages: a Disease Modifying Mechanism in Rheumatoid Arthritis and Systemic Lupus Erythematosus?" which will be published soon in *Annals of New York Academy of Sciences*. He is also a coauthor of two chapters in books that are in press: (1) "The Neuroendocrine Axis in Rheumatoid Arthritis" and (2) "Ovarian and Sympathoadrenal Hormones, Pregnancy, and Autoimmune Diseases."

A Visiting Fellow from India, who is working in the Inflammatory Joint Diseases Section, presented a report at the annual meeting of the American Society for Human Genetics, in Denver, Colorado, in October 1998. She is also an author on two other reports: (1) An Integrated Rat Genetic Map: Analysis of Linkage Conservation With the Mouse and Human Maps and (2) Localization in Rats of Genetic Loci Regulating Susceptibility to Experimental Erosive Arthritis and Related Autoimmune Diseases. Both reports will be published in *Transplantation Proceedings*.

Lymphocyte Cell Biology Section

The Lymphocyte Cell Biology Section continued an active collaboration with the University of Brescia, Italy, to study patients with immunodeficiency. In November 1997, the Section Chief visited the Bone Marrow Transplantation Unit in Brescia and gave a lecture.

A Max Kade Fellow from Austria, a Visiting Fellow from France, and a Visiting Associate from Italy won the NIH Fellows Award for Research Excellence, in 1998. A Visiting Associate from Italy published a report in the *Journal of Immunology,* in May 1998.

Signal Transduction Group

The Head of the Signal Transduction Group and a scientist from Institut Pasteur, Paris, France, are collaborating on studies involving regulation of the immunoinflammatory cytokine tumor necrosis factor α in mast cells. These studies have demonstrated that production of this cytokine requires a mast cell–specific transcription factor that binds to the promoter of tumor necrosis factor α and induces gene transcription. The researchers have identified a novel mast cell–specific transcription factor that may be useful as a therapeutic target in inflammation.

The Signal Transduction Group also initiated joint research with a scientist at the National Institute of Medical Research, London, England, to study the role of a hematopoietic cell–specific protein in inflammation.

A Visiting Scientist from Israel discovered two proteins that regulate the growth and differentiation of mast cells. These studies may be important to the treatment of diseases involving excessive proliferation of mast cells.

Bone and Connective Tissue Biology Branch

Craniofacial Development Section

The Craniofacial Development Section continues to collaborate with scientists at Tohoku University, Japan, on the study of regulatory mechanisms of extracellular matrices on the phenotypic expression of chondroblasts and osteoblasts.

A Senior Staff Fellow received a Short-Term Visiting Research Grant from NIH and the Japanese Society for the Promotion of Sciences Joint Program, to perform collaborative research at Tohoku University.

A Visiting Fellow from Japan studied the relationship of biomechanical forces on early chondrogenesis and developed a unique three-dimensional system for cell culture in collagen gel. His work was reported in an article, "Compressive Force Induces Sox9, Type II Collagen and Aggrecan and Inhibits IL1-β Expression Resulting in Chondrogenesis in Mouse Embryonic Limb

Bud Mesenchymal Cells," which was published in the *Journal of Cell Science,* in June 1998.

A Visiting Fellow from Japan is investigating the molecular signals for migration and differentiation of cranial neural crest cells. He generated a novel method for delivery of genes by adenovirus, to organ cultures of mouse embryos. His work was reported in an article, "Adenovirus Mediated Ectopic Expression of Mxs2 in Even-Numbered Rhombomeres Induces Apoptotic Elimination of Cranial Neural Crest Cells in Ovo," which was published in *Development* and was awarded the Fellows Award for Research Excellence, from NIH.

A Visiting Fellow from Japan continued examining mutations in the FGFR2 gene in relation to craniofacial and skeletal malformations. The investigator detected preferential expression of FGFR2 protein in the chondrocytes at the base of the cranium of the developing mouse skull, and he generated transgenic mouse lines to model Apert's syndrome, a human genetic disorder.

A Guest Researcher and a Visiting Associate, both from Japan, continued to investigate the molecular signals for early chondrogenesis. They reported that the growth factor BMP4 induces chondrogenesis in the developing mandible by upregulation of the activator Sox9 and the repressor Msx2, which, in turn, act antagonistically. This phenomenon can be antagonized by another growth factor, EGF.

Two Visiting Fellows from Japan are engaged in the cloning and characterization of novel genes regulating early morphogenesis of teeth.

Laboratory of Physical Biology

The Chief of the Laboratory of Physical Biology initiated a collaboration with the University of Zürich, Switzerland, to investigate the role of nebulette, a heart-specific nebulin-like protein, in the assembly of contractile apparatus in cultured heart muscle cells.

A Visiting Fellow from Nepal is working on the role of nebulin in the regulation of muscle contraction.

Macromolecular Biophysics Section

The Macromolecular Biophysics Section is collaborating with the Institute of Chemical Pharmacology, University of Innsbruck, Austria, on radiation studies of emopamil binding; with McGill University, Montreal, Quebec, on radiation studies of phenylalanine hydroxylase; and with BioMega Inc., Montreal, on radiation studies of ribonucleotide reductase.

Muscle Biophysics Section

An Intramural Research Training Award (IRTA) Fellow from China expressed and studied the protein-binding properties of defined regions of N-RAP, a novel muscle protein with sequences homologous to those of nebulin. His work defined binding sites of N-RAP for several proteins localized along with N-RAP at the myotendinal junction and yielded information about the physical size of the mouse N-RAP gene. His work on N-RAP was presented at the annual meeting of the American Society for Cell Biology, in Washington, D.C., in December 1997, and at the annual meeting of the Biophysical Society, in Kansas City, Missouri, in February 1998.

A Visiting Fellow from China studied the interactions of nebulin fusion proteins with actin filaments. His work on nebulin was presented at the annual meeting of the Biophysical Society, in Kansas City, Missouri.

A Visiting Scientist from China worked on x-ray diffraction from fully functioning skeletal muscle and successfully identified for the first time the biochemical states of myosins arranged in ordered helical arrays in relaxed muscle.

Another Visiting Fellow from China pursued molecular modeling of skeletal muscle and analyzed the x-ray diffraction patterns to establish the three-dimensional motif of myosins binding to actin in rigor muscle. An IRTA Fellow from China studied the mechanism of regulation in skeletal muscle, particularly the structural role of troponin.

A senior investigator continued joint research with the Hannover Medical School, Germany, and the Deutsches Electronen-Synchrotron, Hamburg, Germany, on the structure–function relationship of skeletal muscle in the presence of nucleotide analogues. The studies were performed at the synchrotron radiation facility of the Deutsches Electronen-Synchrotron.

Laboratory of Skin Biology

Genetic Studies Section

The Genetic Studies Section continued to collaborate with the following researchers:

- an oral surgeon at the University of Rostock, Germany, to study Gorlin's syndrome;
- dermatologists at Istituto Dermopatico dell'Immacolata, Rome, Italy, to identify genes involved in several disorders of cornification; and
- investigators at Hôpital Beaumont, Lausanne, Switzerland, to genotype DNA from families with erythrokeratodermia variabilis.

The Chief and a staff scientist, in collaboration with an investigator at Brown University, Providence, Rhode Island, traveled to Cairo, Egypt, in February 1998, to pursue research on hereditary skin disease in Egypt and to develop DNA-based genetic diagnostic capabilities at Ain-Shams Medical Genetics Clinic. This project is funded by a $50,000 grant from the U.S.-Egypt Joint Science and Technology Fund.

The Section also hosted two Visiting Fellows in fiscal year 1998, one from Germany and one from Ukraine. Each investigator is involved in studies of hereditary skin disease or related diseases.

Molecular Biology of Keratinization Section

The Molecular Biology of Keratinization Section continues to collaborate in the following international research:

- studies of the function of transglutaminases on membrane surfaces, with the University of Debrecen, Hungary;
- studies of the expression and function of transglutaminases in epidermal differentiation and apoptosis, with the University of Rome, Tor Vergata, and Biochemistry Laboratories of Istituto Dermopatico dell'Immacolata, Rome, Italy;
- studies of the biophysical and solution structures of transglutaminase substrates, as visualized by nuclear magnetic resonance and x-ray crystallography, with the University of Rome, Tor Vergata, Italy, and the Institute of Fundamental Sciences, Massey University, Palmerston North, New Zealand;
- studies of the structure of intermediate filaments, with the Institute of Fundamental Sciences, Massey University, Palmerston North;
- biophysical and solution structures of intermediate filament coiled coils, as visualized by nuclear magnetic resonance and x-ray crystallography, with the Maurice Müller Institute, University of Basel, Switzerland; and

- studies of the role of transglutaminase substrates in barrier function, with Hôpital Beaumont, Lausanne, Switzerland.

A Professor of Biochemistry with appointments at the University of Rome, Tor Vergata, visited the Section to discuss and participate in ongoing collaborative projects on transglutaminases and their substrates. The Head of the Institute of Fundamental Sciences, Massey University, Palmerston North, visited to discuss and participate in ongoing collaborative projects on intermediate filaments and their associated proteins.

A Visiting Scientist from Bulgaria is studying the postsynthetic modifications of several epidermal structural proteins. A Visiting Fellow from China is investigating the structures of keratin intermediate filaments. A Visiting Fellow from Hungary is examining the structures of transglutaminases and their interactions with membranes. Four Visiting Scientists from Korea are studying the expression and function of transglutaminase substrates, the structure and function of transglutaminases and their substrates, the regulation of epidermal gene expression, and genes encoding enzymes involved in postsynthetic modifications of skin proteins.

Laboratory of Structural Biology Research

The Laboratory of Structural Biology Research continues to collaborate in several international research efforts, including studies with the following institutions:

- Commonwealth Scientific and Industrial Research Organization, Geelong, Australia, and Massey University, Palmerston North, New Zealand, to investigate the structure of "hard" α-keratin filaments;
- Bach Institute, Moscow, Russia, to pursue protein-engineering projects by using structural elements from bacteriophage tailfiber protein;
- Medical Research Council, Institute of Virology, Glasgow, Scotland, to investigate the capsid structure of oyster herpesvirus, an evolutionarily remote herpesvirus; and
- Centro Nacional de Biotecnologia, Madrid, Spain, to perform electron microscopy studies of human astrovirus.

A Visiting Fellow from Canada studied the polymerization properties of the REV protein of human immunodeficiency virus and is working on the hepatitis B virus assembly. A Visiting Associate from China successfully carried out numerous electron microscopy projects, including high-resolution work on hepatitis B core antigen, cytomegalovirus, actomyosin filaments, and nucleoprotein filaments involved in mutagenesis and repair of DNA. A Visiting Fellow from the Czech Republic performed electron microscopic and biochemical studies of the assembly of the cornified cell envelopes of terminally differentiated keratinocytes. A Visiting Fellow from France analyzed the three-dimensional structure of the energy-dependent Clp protease of *Escherichia coli.* An IRTA Fellow from India is performing research on image-processing of structural transitions of virus capsids. A Visiting Fellow from Japan continued the ClpAP protease project with a view to extending the visualization of the three-dimensional structure. Another Visiting Fellow from Japan started work on a virus-engineering project. A Visiting Associate from New Zealand developed a novel image-processing technique to extend the resolution of three-dimensional reconstructions of electron micrographs of viruses and applied them successfully to hepatitis B virus core antigen.

VIII.
National Cancer Institute

INTRODUCTION

The National Cancer Institute (NCI), in cooperation with extramural institutions and the Fogarty International Center of the National Institutes of Health (NIH), supports international health research through bilateral agreements, grants, and contracts. The Institute supports about 2,300 intramural research scientists and staff, some 1,000 Visiting Scientists and Exchange Scientists, and about 5,000 extramural grants, contracts, and training awards. The work of outstanding scientists is supported through fellowships, cooperative projects, exchanges of personnel and materials, and workshops. During fiscal year 1998 (FY 98), NCI obligated approximately $45 million for foreign grants and contracts, the NIH Visiting Program, bilateral scientist exchanges, workshops, and international dissemination of cancer information.

NCI's international effort, coordinated by the Office of International Affairs (OIA) in the Office of the NCI Director, works in conjunction with programs at other NIH Institutes and the Fogarty International Center. Advances in cancer research result from NCI support and from support by other U.S. and foreign government agencies, industries, private nonprofit institutes, and individual philanthropists. Individual scientists initiate most of the cooperation in cancer research here and abroad, and other institutions also support international activities directly, without NCI involvement. NCI does take the initiative, however, when it is expedient to exploit a scientific opportunity. The research divisions within NCI are the Division of Basic Sciences, the Division of Clinical Sciences, the Division of Cancer Biology, the Division of Cancer Epidemiology and Genetics, the Division of Cancer Prevention, the Division of Cancer Control and Population Science, and the Division of Cancer Treatment and Diagnosis.

International Workshops

One way in which OIA fosters joint research between U.S. and foreign scientists is by cosponsoring international workshops. The OIA workshops program brings together small groups of U.S. and foreign scientists who are at the forefront of their fields of research, to discuss their newest research that has not yet been published.

The U.S.-Japan Cooperative Cancer Research Program is a joint program of NCI and the Japan Society for the Promotion of Science. As is customary under the program, several workshops were held in FY 98:

- Genetic Diagnosis of Cancer;
- High-Dose Chemotherapy With Support of Hematopoietic Stem Cells;
- Molecular Epidemiology of Cancer;
- Molecular Determinants of Preneoplasia and Early Cancer Progression;
- Cell Cycle Regulation; and
- Angiogenesis and Cancer.

Other workshops cosponsored by OIA included the following:

- Clinical Trials in Childhood Cancer (Beijing, China);
- Molecular Virology and Molecular Immunology (Shanghai, China);
- Control of Proliferation in Normal and Cancer Cells (New Delhi, India); and
- Chemoprevention in the Age of Genetic Diagnosis (Haifa, Israel).
- In addition, OIA sponsored the attendance of participants at a symposium on Free Radicals in Health and Disease (Jerusalem, Israel, and Amman, Jordan) and at the meetings of the North American Association of Cancer Registries (Vancouver, British Columbia); the International Association of Cancer Registries (Atlanta, Georgia); and the Second National AIDS (acquired immunodeficiency syndrome) Malignancy Conference (Bethesda, Maryland).

Scientist Exchange and Other Training Programs

The Scientist Exchange Programs bring U.S. and foreign scientists together for either short-term (less than 1 year) or long-term cooperation. Long-term exchanges are supported by NCI and the European Organization for Research and Treatment of Cancer (EORTC); NCI and the Japanese Foundation for Cancer Research; and the Oncology Research Faculty Development Program.

TABLE VIII-1.

NCI Office of International Affairs: Exchange Scientists Exchanges, Fiscal Year 1998

Country or Area	No. of Visits	Months
Argentina	1	0.5
Belarus	1	11.0
Brazil	1	1.0
Bulgaria	1	11.0
China	22	147.5
Colombia	1	12.0
Côte d'Ivoire	1	3.0
Egypt	7	30.4
Estonia	1	12.0
France	1	4.0
The Gambia	1	9.0
Georgia	1	1.0
Greece	2	8.5
Germany	3	27.7
Hungary	2	16.0
India	4	25.0
Israel	5	22.9
Italy	4	29.0
Japan	10	74.0
JSPS[a]	12	5.1
Jordan	1	1.0
Korea	6	23.0
Mexico	1	2.2
Morocco	1	6.0
The Netherlands	1	10.7
Pakistan	1	10.0
Poland	1	3.0
Russia	15	88.0
Sweden	3	4.7
Slovakia	1	3.5
South Africa	2	3.3
Spain	2	20.0
Turkey	2	7.0
Ukraine	3	30.5
United Kingdom	1	11.0
Vietnam	4	4.7
Total	**126**	**679.2**

[a] Brief visits sponsored by the Japan Society for the Promotion of Science (JSPS).

TABLE VIII-2.

Foreign Scientists at NCI Under NIH Visiting Program, Fiscal Year 1998

Country or Area	No. of Scientists
Algeria	2
Argentina	9
Australia	18
Austria	5
Bangladesh	2
Belgium	3
Brazil	7
Bulgaria	2
Burkina Faso	1
Canada	22
Chile	3
China	1
Colombia	3
Costa Rica	1
Croatia	3
Cyprus	1
Czech Republic	2
Denmark	4
Egypt	1
Fiji	1
Finland	2
France	28
Germany	43
Greece	6
Hong Kong	1
Hungary	12
India	40
Iran	3
Ireland	2
Israel	9
Italy	39
Japan	110
Jordan	1
Korea	56
Lebanon	2
Malaysia	1
Mexico	6
The Netherlands	13
Nigeria	1
Pakistan	4
Poland	7
Portugal	1
Romania	1
Russia	26
Senegal	1
Serbia-Montenegro	1
Singapore	1
Slovakia	6
South Africa	2
Spain	24
Sweden	3
Switzerland	3
Thailand	1
Tunisia	1
Turkey	8
Ukraine	1
United Kingdom	19
Venezuela	1
Zimbabwe	1
Taiwan	11
Total	**660**

OIA sponsors two programs for development of faculty in oncology research. These are long-term programs for young but established scientists from cancer research laboratories in developing countries. The programs are designed to prepare these scientists for independent careers as investigators and for leadership positions in cancer research in their country. Foreign cancer research institutes nominate a limited number of scientists to the OIA selection committee. Each year, up to 16 candidates are accepted in NCI-supported laboratories. Directors of NCI-designated cancer centers can nominate an additional 16 candidates from developing nations for training at their institutions. The cost of these programs is shared by NCI and the sponsoring laboratory or cancer center.

During FY 98, OIA shared the costs of supporting 126 Exchange Scientists from 35 countries, for a total of 679.2 person-months, through the short- and long-term exchange programs. The distribution of these scientist exchanges for FY 98 is shown in Table VIII-1.

In addition to the Exchange Scientists supported by OIA, 660 foreign scientists visited NCI laboratories under the NIH Visiting Program (Table VIII-2). NCI also contributed to the funding of more than 100 short-term International Cancer Technology Transfer Fellowships, a program administered by the International Union Against Cancer (UICC).

Each year, individuals from a number of foreign countries participate in the Cancer Prevention and Control Academic Course, offered by the Division of Cancer Prevention. In FY 98, participants included representatives from Bulgaria, Chile, China, Korea, and Vietnam.

Cancer Registration in Developing Countries

Population-based cancer registries collect information on all cases of cancer in a defined geographic area, to estimate cancer incidence rates in the general population by variables such as gender, age, cancer site, and stage of disease. The establishment of cancer registries is a critical first step in public health planning, assessment of facility and manpower needs, research, and establishment of effective cancer control programs.

OIA sponsored attendance of personnel from developing countries at registry training courses conducted by the International Agency for Research on Cancer (IARC) and the International Association of Cancer Registries in Lyon, France; Nouméa, New Caledonia; Johannesburg, South Africa; and Atlanta, Georgia. Participants included personnel from Micronesia, Nigeria, Palestine, Tahiti, Uganda, and Zimbabwe.

In cooperation with the Middle East Cancer Consortium, OIA has sponsored cancer registry training programs in Bethlehem, Israel (West Bank), and Amman, Jordan. Training programs have also been held in Santa Cruz, Bolivia; Shanghai, China; and Trivandrum, India. The course in Bolivia was attended by participants from Argentina, Bolivia, Brazil, Colombia, Costa Rica, the Dominican Republic, Mexico, and Peru.

In addition to training, OIA is providing assistance in development of infrastructure to cancer registries in Nigeria, Swaziland, Yemen, and Zimbabwe.

Cancer Information Dissemination

International dissemination of information on cancer research and treatment is a high-priority activity for NCI. In 1990, OIA began information dissemination projects at cancer centers in developing countries, to provide access to the latest published cancer research literature and treatment information through the NCI databases CancerLit and PDQ (Physician Data Query). NCI provided free subscriptions to these two databases on compact disk for a limited time, and the host institute provided the necessary computer hardware. By 1994, more than 50 information dissemination sites were in operation worldwide. With increasing availability of the Internet to access these databases, the compact disk program was discontinued.

The increasing availability of electronic telecommunications networks, even in many countries with an otherwise poor communications infrastructure, is revolutionizing the means by which individuals can access biomedical research and treatment information. The MEDLINE database of the National Library of Medicine (NLM) is freely available on the Internet, either on the Grateful Med system (http://igm.nlm.nih.gov) or via PubMed (http://www.ncbi.nlm.nih.gov/PubMed/). Most of the PDQ database is available via the World

Wide Web site, CancerNet (http://cancernet.nci.nih.gov). The entire CancerLit bibliographic database is available through the CancerNet Web site. In a typical month in 1998, 220,000 user sessions were logged on the CancerNet Web site. About 10% of the users were from outside the United States and Canada.

PDQ information summaries on cancer prevention, screening, treatment, and supportive care can be obtained from CancerFax, an automatic fax-back service, and CancerMail, an electronic mail (e-mail) service. The summaries on treatment and supportive care are available in Spanish, either directly from NCI or from the University of Chile, Santiago. These services also offer monthly CancerLit searches on selected cancer topics. The NCI Liaison Office in Brussels, Belgium, collects information on clinical protocols from Europe for the PDQ database. PDQ is distributed by EORTC through EuroCODE, an electronic communication network for European oncologists.

To use CancerFax, the telephone on a fax machine is used to call 1-301-402-5874 and recorded instructions are followed to retrieve documents. To access CancerMail, users send e-mail messages containing codes for desired documents to the NCI computer and receive the requested information in return. A contents list can be obtained by sending e-mail to cancermail@icicc.nci.nih.gov with the word "help" as the message. CancerMail information also is available via Internet on a number of gopher servers, World Wide Web servers, and other secondary distribution sites.

Unfortunately, because many areas of the developing world do not have full, interactive Internet connections, powerful resources such as the World Wide Web are not yet available. However, most regions do have capabilities to send and receive Internet e-mail (e.g., by telephone or modem) to a commercial or academic service provider. For regions without full Internet access, OIA has encouraged the use of a retrieval system called BITNIS (Batch Internet-NLM Intercommunication Service) to access cancer information through e-mail. BITNIS has been widely used in Latin America and has been introduced to developing countries in Asia, Eastern Europe, and elsewhere

With the American Cancer Society and the Pan American Health Organization (PAHO), OIA cosponsored the production of a Spanish-language edition of the American Cancer Society *Textbook of Clinical Oncology,* which is being distributed free to many of the major medical libraries in Spanish-speaking countries and is being sold at a subsidized rate to medical practitioners there.

In collaboration with the American Health Foundation of New York and PAHO, OIA is cosponsoring the development of a Spanish edition of the elementary school (kindergarten through grade 6) health education program "Know Your Body," for use both in U.S. Latino schools and in foreign schools where Spanish is spoken. A translation into Polish is in process, and translations into other languages are planned. OIA previously supported an Israeli Health Education Scholar at the American Health Foundation, thus facilitating the introduction of a Hebrew and an Arabic version of "Know Your Body" into Israeli and Palestinian schools.

NCI has many collaborative research agreements with IARC. One agreement addresses the identification of agents and exposures that may pose a carcinogenic risk to humans. Monographs containing the results of risk evaluations are published by IARC as individual volumes.

NCI is providing memberships in its Information Associates Program to approximately 45 libraries in foreign cancer centers or medical schools in Africa; Asia, including the Near East; the Caribbean; Central and Eastern Europe; and Latin America. This program, developed by the International Cancer Information Center, provides subscriptions to the *Journal of the National Cancer Institute* (JNCI) and *JNCI Monographs;* access to the PDQ database and to CancerLit digests of citations and abstracts via electronic bulletin board or Internet connection; and a variety of other cancer information services.

Distribution of a "Cancer Seminars" series on videotape is continuing. Copies of these lectures are distributed to 110 foreign cancer institutes, giving young foreign scientists the opportunity to access the latest findings in cancer research. Recent lectures include the following:

- Immune Response to Self and Mutated Human Cancer;
- Genetics of Wilms' Tumor and Insights Into Responses to Chemotherapy;
- Cell Life and Cell Death;
- Genetic Control of Programmed Cell Death in C. (*Caenorhabditis*) *elegans;*
- Human Retroviruses in the Second Decade: Progress Report and Future Perspectives;
- New Directions in Angiogenesis Research;
- Regulation of Human Lymphocyte Recruitment: Basic Principles in Relevance to Disease;
- Present and Future of Small Non–Cleaved Cell Lymphomas;
- Emergence of Resistant Fungal Pathogens in Patients With Cancer and HIV (human immunodeficiency virus) Infection; and
- Therapeutic Implications of Cell Cycle Checkpoints and Apoptosis.

Clinical Trials and Preclinical Drug Development

NCI facilitates international cooperation in clinical trials involving U.S. industry, which sometimes contributes pharmaceutical agents for such trials at no cost to the U.S. Government or foreign collaborating institutions. For example, clinical trials are being conducted in parallel in the United States and at the Russian (former All-Union) Cancer Research Center, Moscow, for the treatment of colon, colorectal, and breast cancers. Patients in these trials are receiving donated leucovorin or granulocyte colony-stimulating factor.

The NCI Liaison Office coordinates the Institute's research and treatment programs in Europe through a formal trilateral agreement with EORTC and the Cancer Research Campaign (CRC) of the United Kingdom. The Liaison Office is involved in the exchange of information, experimental drugs, and research protocols and in programs for international exchange of scientists.

The Liaison Office collects, reviews, and submits European research protocols for inclusion in PDQ, which is distributed worldwide through various channels, including EORTC's EuroCODE. The Liaison Office participates on committees and in working groups involved in all aspects of cancer research and drug development throughout Europe. The Office also facilitates international exchange of experimental drugs for treating cancer, seeks new agents with therapeutic potential from European sources, and assists in the development of research protocols that ensure comparability between data gathered in Europe and in the United States. This comparability has resulted in recognition by the U.S. Food and Drug Administration of data from European drug trials. The EORTC-NCI Exchange Program, administered by the Liaison Office, offers support for up to 3 years for scientists from Europe or the United States to conduct research in an overseas laboratory. NCI also supports short-term scientific exchange with European investigators involved in drug discovery and development. These exchange programs have fostered closer working relationships between European and U.S. investigators and have expedited development of several high-priority new compounds under study in Europe and the United States.

There is a long history of individual overseas institutions participating in the Clinical Trials Cooperative Group Program. Not all participating institutions receive financial assistance from NCI for this research; many investigators participate for the intellectual and emotional satisfaction of doing so, and their institutions subsidize the research. Participants involved in the Cooperative Group program include the following:

- American College of Surgeons Oncology Trials Group (Canada, Germany, Switzerland, and United Kingdom);
- Cancer and Leukemia Group B (Canada);
- Children's Cancer Group (Australia and Canada);
- Eastern Cooperative Oncology Group (Australia, Canada, Israel, and South Africa);
- Gynecologic Oncology Group (Canada);
- Intergroup Rhabdomyosarcoma Study (Canada);
- National Surgical Adjuvant Breast and Bowel Project (Australia and Canada);
- National Wilms' Tumor Study Group (Canada);
- North Central Cancer Treatment Group (Canada);
- Pediatric Oncology Group (Canada and Switzerland); and
- Radiation Therapy Oncology Group (Australia, Canada, and Scotland).

Working with the NIH Office for Protection From Research Risks, staff of the Cancer Therapy Evaluation Program (CTEP), NCI, developed a model for International Cooperative Project Assurance (ICPA) that can be used by foreign groups to participate in the Cooperative Group research protocols. This model will simplify and speed the collaborative process. In the past, if a foreign research group wanted to collaborate with a Cooperative Group, each institution in the group had to apply to the Office for Protection From Research Risks for assurance for each project. Under the ICPA procedure, a single project assurance application from a central body such as a Ministry of Health covers all institutions involved. Since their inception, ICPAs have been awarded to CRC, in the United Kingdom, and to EORTC, in Brussels, Belgium. ICPAs are under negotiation with groups in Brazil and Chile.

CTEP continues to provide investigational anticancer agents to international researchers for Cooperative Group trials and selected clinical trials. In addition to the Cooperative Group studies, a clinical study of azacitidine is under way in Hong Kong, China, and two trials of bryostatin 1 are being conducted by CRC, in the United Kingdom. CTEP staff have participated in a joint project with EORTC, the National Cancer Institute of Canada, and the World Health Organization (WHO), to produce common, standardized response criteria for clinical investigations. In addition, CTEP staff have worked to revise the Common Toxicity Criteria used for grading of adverse events during clinical trials, and their draft proposal will serve as the basis for an initiative to adopt new international criteria.

CTEP has increased international joint efforts in development of cancer treatment with the National Cancer Institute of Canada; the EORTC New Drug Development Office, in Amsterdam, the Netherlands; CRC in the United Kingdom; and a phase I and II clinical trial group based in Milan, Italy, which involves investigators from France, Italy, and Switzerland.

The Developmental Therapeutics Program (DTP) searches for drugs for the treatment of cancer and of AIDS. Through the NCI Liaison Office in Brussels, more than 2,000 compounds per year come from European sources to DTP for screening of therapeutic agents. At least four of the agents in preclinical development leading toward clinical trials for cancer or AIDS originally came from Japan. One of these, a benzoylphenylurea from Ishihara Sangyo, involved very active collaborative research in which the company provided a number of prodrugs. For many years, there also has been formal collaboration in drug development with CRC in the United Kingdom and EORTC. DTP carried out the formulation, development, and production of clomesone, bryostatin, and rhizoxin, which had their initial clinical study in Europe. In addition to these project areas, DTP collaborates with investigators in Europe and Japan who have expertise in the selection of candidate agents for screening. Project areas include cyclin-dependent kinase inhibitors (France and Germany); antiangiogenesis compounds (Italy); benzothiazoles (CRC, United Kingdom); and polymer-delivered therapeutic agents (United Kingdom).

International Cooperative Biodiversity Groups strive to achieve the interdisciplinary and synergistic goals of promoting biodiversity conservation, drug development, and economic growth. This initiative is cosponsored by the National Science Foundation; the Fogarty International Center; the National Institute of Allergy and Infectious Diseases; the National Heart, Lung, and Blood Institute; and the National Institute of Mental Health.

The International Cooperative Biodiversity Group Program supports broadly based, international interdisciplinary projects to meet each sponsoring agency's missions and objectives in four general areas:

1. collaboration in drug discovery and development for diseases of concern to both developing and developed countries;
2. development of inventories of native species and indigenous knowledge;
3. training directed to the needs of an individual country; and
4. improvements in the scientific infrastructure of the host country.

Five projects coordinated by U.S. institutions and involving partnerships with pharmaceutical companies and organizations in seven developing countries were started in September 1998.

The DTP Natural Products Branch has a program of plant collections in Africa and Southeast Asia. The work is coordinated through contracts with the Missouri Botanical Garden, St. Louis (Africa); the New York Botanical Garden, New York (Central and South America); and the University of Illinois at Chicago (Southeast Asia). In Central and South America, there are direct collaborative activities with organizations in Brazil, Costa Rica, Mexico, and Panama. Joint efforts also have been established with groups in China, Iceland, Korea, Pakistan, South Africa, and Zimbabwe. Collection of marine organisms in the Indo-Pacific region is performed through contract with the Coral Reef Research Foundation. Direct cooperative studies of marine organisms have been established with groups in New Zealand and South Africa.

License agreements have been negotiated with countries that are a source of naturally occurring biological materials found through NCI's drug-discovery program. Three compounds have demonstrated highly significant inhibitory activity in vitro against HIV. Two possible anti-HIV agents, calanolide and conocurvone, were isolated from plant material obtained under the NCI Natural Products Program, from western Australia and Malaysia, respectively. In addition, NCI provides screening results to the countries where the material was collected, as well as invitations to scientists from the source countries to join NCI-supported U.S. scientists in the study of plants with potential for therapeutic activity that were collected within their borders. All expenses are paid by NCI. Agreements have been reached with organizations in Bangladesh, Ecuador, Gabon, Ghana, Laos, Madagascar, Malaysia, Palau, the Philippines, Tanzania, Vietnam, and Zimbabwe. Additional joint agreements are in place with the South American Office for Anticancer Drug Development and University Paulista, Brazil; Kunming Institute of Botany, and the Hong Kong University of Science and Technology, China; Instituto Nacional de Biodiversidad, Costa Rica; the University of Iceland; the Korean Institute of Science and Technology; Instituto de Quimica, Mexico; H. E. J. Research Institute of Chemistry, Pakistan; Universidad de Panama; and the South African Council of Scientific and Industrial Research.

The DTP Biological Testing Branch has collaborated actively with a number of foreign investigators in developing and refining the panel of in vitro human tumor cell lines for screening of anticancer agents. For example, human tumor specimens have been provided by investigators from the University of Freiburg, Germany, and the Mario Negri Institute, Milan, Italy. Investigators at these institutions, in turn, participate with DTP in the evaluation of promising antitumor drugs. The agreement with CRC and EORTC has permitted the free flow of material and information for the assessment of compounds provided through the European group. This has resulted in a number of significant joint research activities leading to the identification and further development of classes of compounds through the use of unique in vitro and in vivo assays.

NCI's Diagnostic Imaging Program is supporting two cooperative agreements with international components. One study is designed to measure clinical tumor response to therapy by using magnetic resonance spectroscopy; the study involves two institutions in the United Kingdom and six in the United States. The second study focuses on determining the practical utility of magnetic resonance imaging in diagnosing and characterizing breast cancer. This collaborative effort will accrue patient data from 14 clinical sites, two of which are located in Germany.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Substantial progress has been made in many areas of basic cancer research. For example, a number of genes involved in specific cancers have been identified, and each new genetic discovery guides the development of specific diagnostic approaches, interventions, and treatments. The improving ability to detect very small tumors and to identify rapidly growing tumors is increasing the potential to treat cancer more effectively and to reduce cancer mortality.

Cancer prevention plays a growing role. There is convincing evidence that about one-third of the cases of cancer in the United States are related to the use of tobacco products and that another one-third may be related to dietary factors. One of the most dramatic advances has been the identification of specific cancer susceptibility genes that can be used to recognize individuals at high risk of developing cancer. The discovery of the BRCA1 gene, which is present in patients who have an inherited form of breast cancer, is a recent example.

During FY 98, NCI supported 44 foreign grants and 17 foreign contracts (Table VIII-3). Also, 41 grants and 7 contracts awarded to U.S. institutions during FY 98 had a foreign component. In addition to awards to extramural institutions, scientists in the NCI intramural laboratories are involved in many joint research projects with foreign investigators, institutions, or both. International cooperation in cancer research has played a key role in virtually all areas of progress in the fight against this disease.

TABLE VIII-3.

NCI Foreign Grants and Contracts, Fiscal Year 1998

Country or Area	Grants	Contracts
Australia	4	–
Belgium	1	–
Canada	22	3
China	–	5
Costa Rica	–	1
Finland	2	1
France	2	–
India	1	–
Israel	4	–
Italy	3	1
Jamaica	–	1
Japan	–	2
New Zealand	–	1
South Africa	1	–
Switzerland	2	1
Trinidad and Tobago	–	1
United Kingdom	2	–
Total	**44**	**17**

Breast Cancer

At the University of Melbourne, Australia, NCI is supporting the establishment of a large registry of Australian multigenerational pedigrees by collection and storage of epidemiologic information on the major recognized and putative risk factors for breast cancer and by performance of follow-up studies. This resource will be made available worldwide for research into the genetic epidemiology, biology, causes, prevention, and treatment of breast cancer. Australia is an excellent country in which to establish a Breast Cancer Family Registry. The size of the population is manageable yet sufficient for a study. Other advantages include ethnic diversity and a highly localized, relatively stable population in which families are usually intact and family members in contact with one another.

Dietary Factors

NCI scientists have been performing a number of research projects on esophageal cancer in China, where the incidence of this malignant disease is the highest in the world. In collaboration with the Chinese Academy of Medical Sciences, two nutritional intervention trials were conducted in Lin Xian, where there is an indication that the population's chronic deficiencies of multiple nutrients may contribute to the high incidence rates. Daily vitamin and mineral supplements lowered cancer rates for patients with esophageal dysplasia and for the general population. A 5-year follow-up of these cohorts has been completed, and investigators are preparing the data for analyses to show whether these early effects of micronutrient supplementation persist. Serum collected in 1985 is being used to investigate the association of micronutrient levels and some infectious conditions (as evidenced by serology) with subsequent esophageal cancer, gastric cancer, and stroke in these cohorts.

In collaboration with the Beijing Institute of Cancer Research, NCI is also conducting a study to determine whether certain treatments, alone or together, can retard or reverse the progression of precancerous gastric lesions. These treatments are amoxicillin and omeprazole to eradicate *Helicobacter pylori;* dietary supplementation with a mixture of vitamin C, selenium, and vitamin E; and dietary supplementation with a garlic preparation. The prevalence of precancerous gastric lesions was much lower in a county in Shandong Province where mortality rates for gastric cancer are low and consumption of garlic is high.

Hereditary Factors

Mutations in the BRCA1 or BRCA2 gene are associated with familial forms of breast cancer, and BRCA1 gene mutations are also implicated in hereditary ovarian cancer. NCI-supported investigators at the University of Toronto, Ontario, are studying the potential risks or preventive properties of hormonal manipulations (oral contraceptives and hormone replacement therapy) and prophylactic surgery (tubal ligation, oophorectomy, and mastectomy) for development of breast and ovarian cancer in carriers of these gene mutations.

Esophageal cancer is the seventh most common cause of cancer death worldwide. Several lines of evidence (family history, familial aggregation, segregation, and cytogenetics) suggest that genetic factors may have an important causative role in this malignant disease. Identification of susceptibility genes may allow screening of populations to identify persons at particularly high risk of esophageal cancer, a population that could then be targeted for prevention strategies (e.g., chemoprevention or early detection). Several studies are in progress or in planning to study these cancers in persons from Shanxi Province, China, where rates of esophageal cancer are among the highest in the world. Investigators have collected tumor tissue and healthy tissue from more than 200 patients. Molecular analyses of a limited number of esophageal cancer specimens are in progress.

Biological Markers

A critical goal for prevention research is the application of new technologies for the detection of biological markers to identify human disease and, perhaps more important, to identify individuals at high risk or predisposition to develop a particular disease. Investigators supported by NCI are studying methods of early diagnosis of liver cancer and possibly its precursor liver lesions. These studies, which are based on detection of the serum marker α-fetoprotein, are being conducted in Haimen County, Jiangsu Province, where the prevalence of liver cancer is high. The availability of this population presents a rare opportunity for examining the histogenesis of liver cancer and improving methods for early diagnosis.

Early Detection

NCI supports the work of investigators at Tata Memorial Hospital, Bombay, India, in a community-based randomized-control evaluation of low-cost methods for early detection of common cancers in women. Breast and cervical cancers account for about 50% of cancer deaths in women in India. Among the diagnostic methods being evaluated are clinical breast examination without mammography, self-examination, and visual inspection of the cervix by trained female health workers. The goal is to reduce mortality by detection and diagnosis of breast and cervical cancer at an early stage. This trial is one of the first of its kind to be conducted in a developing country, and findings may be relevant to other countries and populations with limited resources (e.g., underserved populations in developed countries).

Cooperation in the Middle East

On May 20, 1996, the Ministers of Health of Cyprus, Egypt, Israel, Jordan, and the Palestinian Authority formed a historic partnership, with the official signing in Geneva, Switzerland, of the Middle East Cancer Consortium (MECC) agreement. NCI played a major role in orchestrating the agreement.

NCI's role in the establishment of MECC is another of the Institute's ongoing efforts to support and encourage cooperation among cancer researchers and practicing oncologists in the Middle East region. In 1994, NCI had a pivotal role in the creation of the Middle East Cancer Society. Whereas MECC is an intergovernmental body, the Middle East Cancer Society is a regional scientific society, a nongovernmental organization that encourages the collaborative efforts of the region's cancer researchers and oncologists.

The aims of MECC are to increase knowledge about cancer and to decrease its burdens for the people of the Middle East. In a region where few countries maintain cancer registries, especially population-based registries, and where cancer statistics are scarce, MECC's main areas of focus include cancer surveillance, information, and education. The consortium also concentrates on training, basic research, enhancement of public health and patient care, quality control, and international communications. On the clinical side, cooperation may involve basic and applied research and may include programs of clinical guidelines and protocols. Membership in MECC will be expanded to include other countries in the region, and other highly developed countries are expected to join the United States in sponsoring this venture.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Cooperative Research Programs

Formal cooperative research programs are governed either by agreements between governments or by agreements between institutes. NCI participates in many of the 94 bilateral agreements that the NIH has with 46 nations, and NCI also has direct agreements with organizations in 14 countries and informal ties with institutions in many more countries. The countries with which NCI has formal or informal agreements are listed in Table VIII-4.

Selected Country-to-Country Activities and Bilateral Agreements

Australia

NCI supports studies at the Walter and Eliza Hall Institute of Medical Research, Melbourne. One project focuses on understanding the external regulation of granulocytes and macrophages at the cellular and molecular levels and on defining the molecular defects in those cells that lead to the formation of myeloid leukemia. In another NCI-supported study at this institute, researchers are investigating oncogene-induced leukemogenesis in transgenic mice.

NCI also supports a project at the University of Queensland to establish a registry of multigenerational pedigrees in Australia and New Zealand, to be used in research on the cause, pathogenesis, and prevention and treatment of colorectal cancer.

TABLE VIII-4.

NCI Cooperative Research Program, Fiscal Year 1998

Direct Bilateral Agreements	Agreements Through FIC		Informal Agreements	
China	Argentina	Kuwait	Bahamas	Morocco
Egypt	Armenia	Mexico	Barbados	Myanmar
France	Australia	Mongolia	Bolivia	Nicaragua
Germany	Austria	New Zealand	Bulgaria	Norway
Hungary	Belgium	Nigeria	Costa Rica	Panama
Israel	Brazil	Pakistan	Denmark	Paraguay
Italy	Canada	Slovenia	Estonia	Peru
Japan	Chile	South Africa	Ghana	Philippines
Korea	Colombia	Spain	Honduras	St. Kitts and Nevis
The Netherlands	Croatia	Sri Lanka	Ireland	Sudan
Poland	Czech Republic	Sweden	Jamaica	Trinidad and Tobago
Romania	Estonia	Switzerland	Latvia	Uganda
Russia	Finland	Thailand	Lithuania	Vietnam
Slovakia	Greece	Turkey		
United Kingdom	India	Ukraine		
EORTC	Indonesia	Venezuela		
	Jordan	Zimbabwe		
	Kenya	Taiwan		

Belgium

NCI provides partial funding to assist the EORTC Data Center, Brussels, in providing statistical assistance and expertise to the clinical cooperative groups of EORTC, which have 200 multicenter trials in progress. NCI also maintains a Liaison Office in Brussels.

Brazil

NCI supports an investigator from McGill University, Montreal, Quebec, who is performing an epidemiologic cohort study of the natural history of human papillomavirus (HPV) infection and cervical neoplasia in a population of low-income women in São Paulo, one of the highest-risk areas worldwide for cervical cancer. Although HPV infection is known to be an important cause of cervical cancer, most of the epidemiologic data have come from retrospective studies, which do not provide information on the dynamics of cervical HPV infection in an individual. This study is testing the hypothesis that persistent infections with oncogenic HPV types are likely to be the true precursor events leading to cervical carcinogenesis. Persistence of infections is being documented by study of molecular variants of HPV, which provides a much finer level of detail than simple HPV typing. In addition, this molecular approach may unveil other prognostic markers of progression, across the spectrum of cervical lesions.

NCI scientists are studying risk factors for perinatal HIV transmission by comparing data from Brazil with results from Africa. The similarities and differences shown by these data may reveal specific practices (e.g., duration of breast-feeding) that could be modified to reduce the risk of perinatal HIV transmission.

Canada

NCI supports research projects at several Canadian universities, cancer centers, and hospitals. Efforts include studies in the following areas:

- cellular thermostability and thermotolerance;
- immunologic and molecular markers for diagnosis and prognosis of bladder cancer;
- improved dosimetry in radiotherapy with photon beams and ^{192}Ir;
- genetic epidemiology of epithelial ovarian tumors;
- psychosocial stress and growth of mammary tumors;
- modification of xenograft radiosensitivity by chemotherapy;
- reduction in fat intake and risk of benign breast disease;
- molecular epidemiology of persistent HPV infection;
- development of primary lung cancer after breast cancer;
- protective effects of dietary supplementation with garlic derivatives in lung cancer;
- quantitation of hypoxic tumor cells;
- plasminogen regulation by annexin II tetramer;
- inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase in treatment of acute myeloblastic leukemia;
- analysis of risk factors for carriers of the BRCA1 or BRCA2 gene; and
- hormone replacement therapy and risk of colon cancer.

At the Ontario Cancer Treatment and Research Foundation, Toronto, NCI is supporting projects on development of population-based registries of familial colon cancer and familial breast cancer. Such registries will serve as resources for future epidemiologic studies, primary prevention trials, genetic studies, and research on surveillance strategies.

NCI is collaborating with investigators at the University of Toronto in genetic analyses of two groups: melanoma-prone families and individuals with multiple primary melanomas who are not known to be members of families at high risk for melanoma. Functional analyses of identified mutations also will be conducted. In addition, NCI scientists are working with the Cancer Division of the Laboratory for Disease Control, Health and Welfare, to evaluate exposure of agricultural workers to pesticides and the effect of protective practices on these exposures.

Several Canadian institutions also participate in many of the NCI Clinical Trials

Cooperative Groups and in other NCI-sponsored clinical trials.

China

NCI collaborates in many projects in China that involve research on the cause, prevention, and treatment of various types of cancer. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

In Shanghai, a randomized trial of breast self-examination is under way in 520 factories of the Shanghai Textile Industry Bureau. The purpose of the study is to determine whether the regular practice of breast self-examination will reduce mortality from breast cancer. Nearly 300,000 current and retired female workers between the ages of 30 and 64 years are participating in this study.

Other NCI studies in China (Haimen County) are focused on early detection of liver cancer. The 5-year survival rates are less than 5% for patients who have a diagnosis of primary hepatocellular carcinoma (PHC) after symptoms appear. Surgical resection of small, asymptomatic tumors, however, has yielded 5-year survival rates as high as 67%. Chronic HBV infection is associated with about 80% of liver cancers. Monitoring serum levels of α-fetoprotein in HBV carriers may permit detection of early-stage PHC. NCI is supporting a controlled trial of α-fetoprotein screening followed by ultrasonography for the early detection of PHC, to be conducted in this area where the prevalence of endemic HBV is high.

A study of biochemical and molecular early markers of lung cancer, which is the leading cause of cancer death in the United States, is being performed in a high-risk population in China. The subjects of the research are underground miners from the Yunnan Tin Corporation, who are at extraordinary risk of lung cancer from exposure to radon, arsenic, and tobacco. More than 7,000 miners receive annual screening by chest x ray and sputum cytology to identify new cases; biological specimens, including sputum samples, are stored for evaluation of potential early markers of lung cancer. The study is being conducted jointly with scientists from the Yunnan Tin Corporation; NCI; Johns Hopkins University, Baltimore, Maryland; and the University of South Florida, Tampa.

A project evaluating the early detection and treatment of esophageal cancer is being conducted in the high-risk population of Lin Xian, in collaboration with scientists from the Chinese Academy of Medical Sciences. The purpose of the research is to identify methods to improve screening, endoscopic localization, staging, and endoscopic therapy in this malignant disease.

PHC is one of the three most common causes of cancer death in the world and accounts for up to 1 million deaths a year. Little is known about the genetic epidemiology of PHC or the specific molecular mechanism responsible for the disease. NCI investigators are conducting studies in a cohort of individuals from China in which the carrier rate for the hepatitis B virus is 12.6%. Hepatitis B virus is thought to be a causative agent of liver cancer. To investigate genetic outcomes, a nested case–control study is being conducted in collaboration with the Zhong Shan Hospital of the 1st Shanghai Medical School and the Qidong City Liver Cancer Prevention Program. The study will correlate the genetic constitution of healthy tissue and tumor tissue in individuals for whom clinical and epidemiologic information is available, to evaluate the joint significance. Statistical methods will be used to evaluate the role of genetic and environmental factors in PHC, and molecular studies are being conducted to determine whether genetic changes observed in tumors are consistent with a tumor-suppressor gene model of oncogenesis.

An NCI project in collaboration with the Ministry of Public Health in Beijing is assessing health risks associated with exposure to indoor radon. Investigators are comparing lung cancer risk due to radon exposure in males and females and are investigating whether exposure to tobacco smoke or other contaminants of indoor air may influence lung cancer risk due to radon exposure.

In Shandong, where stomach cancer rates are high, NCI is supporting a project to identify and evaluate determinants of gastric dysplasia, intestinal metaplasia, and chronic atrophic gastritis, which are thought to be precursors of stomach cancer. Rates of transition of these gastric lesions to cancer have been determined in a 6-year follow-up. The incidence of stomach cancer in patients with intestinal metaplasia or dysplasia was 30-fold higher than that in subjects with chronic atrophic gastritis. Studies are planned to determine whether inherited polymorphisms or somatic mutations are predictive of transition rates in precancerous gastric lesions.

Several descriptive studies are planned to investigate trends in cancer rates in China and elsewhere. NCI plans a joint study with the Cancer Institute of the Chinese Academy of Medical Sciences to compare mortality rates for various types of cancer in 1990–1992 with rates from an earlier exhaustive survey in 1973–1975. NCI researchers are collaborating with researchers at the Shanghai Cancer Institute to analyze trends for cancer incidence in 1972–1994 in the Shanghai region and to try to correlate such changes with changes in lifestyle factors and environmental exposures.

A population-based case–control study was conducted in Shanghai to investigate reasons for the extremely low risk of prostate cancer in this population. (The risk of prostate cancer is now increasing.) Data from this study are being analyzed. Scientists are addressing a variety of hypotheses, which are related to hormone levels, dietary intake, anthropometry, and medical practice. They are using both interviews and biological information. The scientists are also investigating whether genetic factors are related to the very low risk of prostate cancer in China.

Costa Rica

A population-based cohort of 10,000 women is having follow-up to study the natural history of HPV infection and cervical neoplasia. The project will define the main causal pathways to cervical cancer precursors; it incorporates new technologies aimed at improving cervical cancer screening. The follow-up of the cohort is now in its 5th year. An adjunct study is being conducted to define immunologic factors that contribute to disease progression. In addition to this effort, NCI is collaborating with Universidad Nacional, Heredia, to evaluate cancer incidence in a cohort of workers exposed to pesticides.

Denmark

NCI supports the work of investigators at the Danish Cancer Society in research using record linkage to identify and quantify the risk of cancer associated with particular occupations and with diagnosis of selected medical conditions or exposure to certain surgical procedures. Unique opportunities to conduct cost-efficient record-linkage studies of causes of cancer are provided by the availability of (a) population-based rosters of patients with diagnosis of various medical conditions and treatment with specific procedures and (b) cancer registry data from the same population.

A population-based record-linkage study of cancer risk in patients with ataxia-telangiectasia and their relatives is being conducted in Denmark, Finland, Norway, and Sweden. The researchers will sequence the gene for ataxia-telangiectasia to identify and characterize mutations in patients with the condition, and they will perform screening for family-specific mutations in relatives.

Finland

At the University of Helsinki, NCI sponsors studies on the natural history and incidence of hereditary colon cancer and research on soybean isoflavonoids and lignans. These diphenolic compounds have been shown in numerous in vitro and animal experiments to have antiproliferative properties in many types of cancer. In addition, they have many other biological effects that make them strong candidates for agents to protect against cancer.

Follow-up continues in the lung cancer prevention project started in Finland in 1984 as a collaborative effort between NCI and the National Public Health Institute of Finland. The main activity has been a study of the effects of α-tocopherol and β-carotene dietary supplements on lung cancer incidence and mortality.

France

At IARC in Lyon, NCI provides support for the IARC Program on the Evaluation of Carcinogenic Risk to Humans. In this project, investigators use published epidemiologic and experimental data to identify chemicals or complex mixtures of chemicals that may pose a carcinogenic risk to humans. The results of data analysis are published in *IARC Monographs*. Also at IARC, NCI supports a project on the role of intercellular communication at the gap junction and mechanisms for its control in multistage carcinogenesis and on the control of cell growth by connexin genes. Scientists from NCI are collaborating with colleagues at INSERM (Institut National de la Santé et de la Recherche Médicale) on a study of possible occupational risks for brain cancer.

Informal cooperation between NCI intramural and extramural scientists—particularly between those at more than 50 NCI-designated cancer centers and their colleagues at the 20 French cancer centers—involves many more persons than the formal programs. In some cases, support for such collaboration has been provided by the French Association pour la Recherche sur le Cancer. The association has made the NCI-developed PDQ database available in French, over Minitel phone terminals.

Germany

In Germany, NCI cooperates mainly with the German Cancer Research Center (Deutsches Krebsforschungszentrum), Heidelberg, and Westdeutsches Tumorzentrum, Essen. Investigators at the research center are working with NCI-supported scientists at Georgetown University, Washington, D.C., on the development of mucosotropic vaccines against HPV and with scientists at the University of Arizona, Tucson, on the overexpression of the gene for tumor growth factor β in malignant squamous cell carcinoma cells. For their work in developing and further refining the panel of in vitro human tumor cell lines that is used for screening of agents for cancer treatment, the Biological Testing Branch, DTP, has received human tumor specimens from investigators at the University of Freiburg.

In collaboration with the National Institute for Occupational Safety and Health, NCI is examining the occurrence of epithelial proliferative lesions and lung cancers, by histologic type, in a large population of uranium miners from the Saxony region in Germany who had heavy exposure to silica, radiation, or both in the 1950s and 1960s.

India

NCI investigators work with the Indian Council on Medical Research, New Delhi, and with the following cancer centers on treatment protocols for lymphoblastic leukemia and nonlymphoblastic lymphomas: Tata Memorial Center, Bombay; the Cancer Institute, Madras; the Kidway Memorial Institute of Oncology, Bangalore; and the Rotary Cancer Center at the All India Institute of Medical Sciences, New Delhi. NCI also cooperates with cancer centers in Chandigarh, Trivandrum, and Vellore.

NCI researchers are collaborating with investigators at the Trivandrum Cancer Centre on an epidemiologic study to evaluate the relationship between pesticide exposure and the risk of progression of breast cancer. In addition, a project to study the mechanisms of action of benzidine is being conducted in collaboration with scientists at the National Institute of Occupational Health.

Israel

Studies at the Weizmann Institute of Science, Rehovot, are aimed at understanding the mechanism of action of the p53 tumor-suppressor gene in its normal (wild type) and mutated forms. Inactivation of the endogenous wild-type p53 gene is associated with more than one-half of all cases of human cancer. Studies are focusing on the identification and characterization of genes involved in p53 regulation. Other NCI-supported projects at the Weizmann Institute address (a) use of magnetic resonance imaging and spectroscopy as noninvasive procedures for early evaluation of breast cancer response to hormonal therapy and (b) investigation of molecular mechanisms through which the ErbB-2/HER2 oncoprotein contributes to tumorigenesis in various adenocarcinomas.

At Tel Aviv University, NCI supports research on the neuroendocrine and immunologic mechanisms underlying the modulatory effects of the estrous cycle, gonadal hormones, and gender on immune competence and tumor development.

NCI is supporting an epidemiologic study of ovarian cancer at the Chaim Sheba Medical Center, Tel Hashomer, to evaluate a broad range of potential risk factors (e.g., reproductive, hormonal, nutritional, genetic, and occupational factors). Genetic analysis is also being added to the study. Scientists are pursuing the possibility of performing a study to assess the role of the BRCA1 and BRCA2 genes in prostate cancer risk, and a study of BRCA1 and BRCA2 gene mutations in male breast cancer is also under way. In addition, a feasibility project is being conducted to ascertain whether ataxia-telangiectasia is hereditary in approximately 24 candidate families and to determine procedures for a population-based study of cancer risk in these families.

Italy

A new joint study by investigators from NCI and the University of Milan has collected 25 pedigrees and biological specimens on kindreds with cutaneous malignant melanoma. This material, in conjunction with a case–control study of melanoma, will provide a means to investigate a genetic component to melanoma in this Mediterranean population. Genotyping of these families is under way. This study will also investigate whether deficits in DNA repair may contribute to development of melanoma.

In an NCI-supported case–control study at the University of Milan, researchers are investigating the molecular epidemiology of cutaneous malignant melanoma, with the hope of developing primary prevention measures against the steadily increasing occurrence of this tumor. The study is exploring the individual and combined influence of sun exposure and proficiency of DNA repair on risk for melanoma. The study site in Italy was chosen because of the prevalence of sun exposure in a large population being served by a single hospital that has a dermatology division with highly experienced staff, to ensure accurate case identification. NCI is also collaborating with investigators from the University of Cagliari, Sardinia, in evaluation of cancer risk among workers who applied pesticide in a campaign to eradicate malaria.

At the European Institute of Oncology, Milan, NCI is supporting a study using plasma insulin-like growth factor I as a potential surrogate marker of contralateral breast cancer in women younger than 50 years of age who are being treated with the synthetic retinoid *N*-(4-hydroxyphenyl)-retinamide (fenretinide). In a related NCI-supported project at the same institute, investigators are examining interactions between low-dose tamoxifen and fenretinide on a set of biomarkers in premenopausal women with minimally invasive (in situ) breast cancer.

NCI is collaborating with investigators at the University of Milan, the Centers for Disease Control and Prevention, and the National Institute of Environmental Health Sciences (NIH), in a study of the effects of dioxin on subjects from Seveso, who were exposed to this environmental toxin after an industrial accident in 1976. Blood levels of dioxin have remained elevated 20 years after exposure. Investigators plan to conduct a case–control study of individuals having cancers that are linked to dioxin exposure (e.g., non-Hodgkin's lymphoma and soft tissue sarcoma).

Jamaica

Since the early 1980s, NCI has been involved in studies of the natural history of infection with human T-cell leukemia/lymphoma virus type I (HTLV-I) and its relationship to adult T-cell leukemia/lymphoma. Several prospective cohorts, particularly in Jamaica and in Trinidad and Tobago, are a source of biological specimens that can be used to investigate important questions in disease pathogenesis. The current emphasis is on studies to evaluate familial and genetic aspects of HTLV-I infection and associated diseases. The families in the study are a high-risk population suitable for continued follow-up to evaluate both environmental and genetic aspects of disease pathogenesis.

In a study of nearly 2,000 Jamaican women, NCI is examining potential risk factors for progression of low-grade cervical intraepithelial neoplasia to risk of cervical cancer. Jamaica was chosen for this investigation because of the high incidence of cervical cancer and the high prevalence of sexually transmitted infections, particularly HTLV-I, in the general population. An earlier study in Jamaica showed that HTLV-I infection was strongly associated with the development of more severe cervical neoplasia. More recent findings show that HTLV-I proviral DNA is detectable in cervical tissue from more than one-half of infected women. Thus it is plausible that direct interaction between HTLV-I and HPV, the principal cause of cervical neoplasia, plays a role in cervical tumorigenesis in women infected with both viruses. Researchers are evaluating tissue samples from women with both these viruses, by using in situ hybridization and immunohistochemistry to further explore this possibility.

Other infectious agents that are detectable in cervical epithelial tissues may also have a role in the development of cervical cancer. Specimens from the Jamaica study are being examined for herpesvirus, chlamydia, and adeno-associated viruses. In contrast to the other agents, adeno-associated viruses may protect against cervical cancer, because of their interference with HPV.

Japan

Six very productive workshops were held during FY 98 under the agreement with the Japan Society for the Promotion of Science. (See also the section on "International Workshops.") There is extensive collaboration between the United States and Japan in therapy using boron neutron capture, particularly in treatment of malignant brain tumors and melanomas. Another area of collaboration is the study of modulation of neoplasia associated with liver fluke parasites, in Nagoya. NCI also supports research on the natural history of HTLV-I, which is highly endemic in the population in southwestern Japan. HTLV-I is a latent retrovirus that causes adult T-cell leukemia/lymphoma in about 1% of all infected persons.

Hepatitis C virus (HCV) is highly prevalent in Japan, which provides a situation conducive to its study. In a cohort study, NCI scientists examined the interactions of HCV and HTLV-I in an area of Japan where both viruses were endemic. Death from liver cancer was strongly associated with antibody to HCV (anti-HCV). Antibody to HTLV-I (anti-HTLV-I) was somewhat correlated with HCV infection but provided no added risk for liver cancer. In related research, investigators studied a cohort of Japanese Americans in Hawaii. All the study participants were descended from persons who had emigrated from Japan before the mid–20th century epidemic of HCV in Japan. In this population, there was a strong association between hepatocellular carcinoma and hepatitis B virus, but not between hepatocellular carcinoma and HCV. This finding differs from current findings in Japan, where 80% of patients with hepatocellular carcinoma have HCV infection.

In collaboration with the Radiation Effects Research Foundation in Hiroshima and Nagasaki, NCI is conducting epidemiologic and multidisciplinary studies of cancer risk in relation to radiation dose among a cohort of atomic bomb survivors. Studies under way include site-specific surveys of the incidence (a) of benign and malignant tumors of the thyroid gland, central nervous system, and ovary, and (b) of cancers of the breast, liver, colon and rectum, lung, and lymphoid tissue, as well as case–control interview studies of patients with thyroid or colon cancer and control subjects. NCI is also collaborating with Japanese investigators who have studied families with Werner's syndrome, to evaluate the unusual melanomas that occur in excess in individuals with this condition.

Malawi

Scientists at NCI and Johns Hopkins University, Baltimore, Maryland, are monitoring perinatal statistics in Malawi to determine whether vaginal cleaning with an antiseptic by hospital staff at delivery of an infant reduces neonatal morbidity and mortality. Investigators are using data gathered from the 7,000 women enrolled in this study, to determine whether cesarean section reduces the risk of HIV transmission and how frequently breast-feeding transmits HIV in this setting. In addition, new studies are under way to examine HIV infection in twins born to infected mothers.

Mexico

NCI is collaborating with the National Institute of Public Health of Mexico to evaluate the relationship between serum levels of organochlorine chemicals, such as DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated biphenyls), and the risk of breast cancer.

NCI is sponsoring studies by an investigator from Stanford University, California, on the role of *H. pylori* infection as a cause of adenocarcinoma of the distal stomach, a cancer with highest incidence in developing countries. Studies are being conducted in Chiapas, a region with high rates of gastric cancer and preneoplasia. Evidence that therapy for *H. pylori* reverses preneoplastic lesions could provide a foundation for gastric cancer screening and prevention trials and could enhance understanding of preneoplasia and inflammation-related carcinogenesis.

The Netherlands

The Division of Cancer Prevention is working with the Department of Public Health, Erasmus University, Rotterdam, to develop a microstimulation model designed to analyze the cost and effectiveness of various screening strategies and methods for the early detection of colorectal cancer.

Cancer risk associated with nasopharyngeal implantation of radium (Crowe method) for treatment of eustachian tube dysfunction is being evaluated retrospectively in a cohort of patients treated at a number of clinics in the Netherlands during the 1940s and 1950s.

Panama

Serological studies have found the human T-cell leukemia/lymphoma virus type II (HTLV-II) to be endemic in some isolated Indian tribes of the Amazon and other regions in the Americas. This finding suggests that HTLV-II is an ancient virus that entered the Western Hemisphere with human migration. NCI has conducted studies on the transmission of HTLV-II and its health effects among the Guaymi Indians residing in Changuinola, the capital of the Bocas del Toro province in western Panama. Transmission appears to resemble transmission for HTLV-I, which is primarily a consequence of breast-feeding and, for women, a result of sexual intercourse. No health consequences of infection with the virus have been clearly identified.

Peru

NCI researchers are working with the Universidad Peruana Cayetano Heredia, Lima, on a descriptive study of recent changes in the incidence and pathology of esophageal cancer and stomach cancer in Peru.

Poland

NCI is collaborating with investigators at the Institute of Oncology, Warsaw, to explore the role of diet as a cause of gastric cancer, which occurs at unusually high rates in Poland. Another study is examining smoking and infection with HPV as cofactors associated with the risk of cervical cancer.

In one joint project, researchers are working to identify factors associated with the high rates of stomach cancer in Poland. In another joint study, scientists are performing molecular studies of lung cancer and laryngeal cancer in regions with severe industrial pollution.

NCI researchers are also involved in a collaborative study to assess and compare risk factors for breast cancer among Polish Americans living in Chicago and Detroit and among women living in Poland. Major areas of interest will be the relationship of risk to dietary patterns, physical activity, and occupational exposures. The influence of these and other factors on genetic predisposition to the disease will also be assessed.

Russia and Other Countries of the Former Soviet Union

Many more requests than can be accommodated are received from scientists in Russia and other countries of the former Soviet Union who want to perform research in the United States. During FY 98, about 60 cancer researchers from these countries came to work in the laboratories of U.S. scientists.

NCI researchers and colleagues from the Jonsson Cancer Center, Los Angeles, California; Dana Farber Cancer Center, Boston, Massachusetts; and Roswell Park Cancer Center, Buffalo, New York, are participating in clinical trials based in Moscow, Russia. Two of the trials use 5-fluorouracil plus leucovorin in the treatment of colorectal carcinoma, and a third uses granulocyte colony-stimulating factor in adjuvant therapy for breast cancer.

NCI investigators are evaluating the relationship between thyroid disease (especially thyroid cancer) and doses of radiation to the thyroid from exposure to radioactive iodine and other radionuclides that were released in the 1986 nuclear power plant accident at Chernobyl. The study subjects are persons in Belarus and Ukraine who were children and adolescents at the time of the accident. The incidence of leukemia and lymphoma among Chernobyl cleanup workers in Ukraine also is being studied. In addition, NCI is cooperating with WHO, the European Commission, and the Sasakawa Memorial Health Foundation of Japan, to establish thyroid tissue repositories in Belarus, Russia, and Ukraine. Also, NCI is collaborating with Japanese and Russian scientists in epidemiologic studies of cancer risk among plutonium workers at the Mayak weapons fabrication plant near Chelyabinsk, Russia, and residents of the Techa River area, in relation to exposure to radionuclides that entered the river from the plant.

NCI is performing a joint study with the St. Petersburg Medical Academy for Postgraduate Training to evaluate occupational factors as a cause of lung cancer and their interaction with genetic susceptibility markers.

A survey of the prevalence of thyroid nodules and cancer has been initiated in relation to radiation dose in a cohort of 2,500 residents of Semipalatinsk, Kazakhstan, who were present as children during a period of substantial radioactive fallout from atomic bomb tests in 1949–1956. Blood samples will be collected to verify dose estimates, and subjects will be clinically examined to verify the presence of thyroid nodules.

Senegal

NCI supports research by an investigator from the University of Washington, Seattle, on cervical neoplasia and HIV infection in Senegal. This research focuses on the role of human immunodeficiency virus type 1 and type 2 (HIV-1 and HIV-2) as risk factors for cervical cancer and its precursor lesions, in this region of the world where people are at very high risk of contracting HIV. Related studies are concerned with the contribution of HPV to the development of cervical cancer. Recent cross-sectional studies have shown HIV infection to be associated with an increased risk of HPV-related lesions. Invasive cervical cancer is now considered an indicator of AIDS in HIV-infected women.

An NCI-supported study in Senegal, where the incidence of PHC is high, is using molecular and biochemical methods to identify viral, genetic, and environmental factors associated with increased risk of developing PHC. This research is being conducted by investigators from Fox Chase Cancer Center, Philadelphia, Pennsylvania. Even though chronic HBV infection is associated with 80% of the cases of PHC in the world, 75% of chronic carriers of HBV do not develop PHC and at least one-half do not develop liver disease. Little is known about the specific environmental, viral, or genetic factors that affect risk of these diseases and how these factors interact.

Singapore

NCI supports an investigator from the University of Southern California, Los Angeles, who is conducting a cohort study of 60,000 Chinese residents of Singapore, aged 45–64 years. The primary aim of the study is to definitively establish the causal relationship between ingestion of Chinese salted fish and similar foods and development of nasopharyngeal carcinoma, as suggested by previous case–control studies. A broader aim is to establish a stable cohort for the long-term study of the relationship of dietary and other environmental determinants to cancer and other chronic diseases. Related projects by the same investigator include (a) a case–control study in Shanghai, China, a region of intermediate risk of nasopharyngeal carcinoma, and (b) a case–control study in Taiwan, a region of moderately high risk. These two studies are a part of the investigator's continuing attempt to define the cause of nasopharyngeal carcinoma in Chinese populations. Incidence rates vary by 20-fold in these populations.

Slovenia

Considerable controversy surrounds the question of whether the two types of asbestos (amphilboles and chrysotile) have different carcinogenic potencies. This issue has been difficult to address because of a lack of quantitative data to estimate separate dose–response curves for the two fiber types. An NCI-supported study by an investigator from the University of Massachusetts, Lowell, is examining risk for lung cancer and for mesothelioma in former employees of a Slovenian asbestos plant. In this study, excellent data on historical exposure to each of the two broad classes of asbestos fibers are available.

South Africa

The injectable contraceptive progestogen (depot medroxyprogesterone acetate [DMPA]) has been used worldwide by more than 11 million women. Concerns exist about breast cancer risk due to use of DMPA, particularly after long-term use. NCI is sponsoring research by an investigator from Boston University, Massachusetts, who is performing a hospital-based case–control study of DMPA-related breast cancer in the western Cape of South Africa, where more than 30% of the nonwhite women have used DMPA—the highest documented exposure in the world.

A related study by the same investigator is being conducted in Cape Town. Carcinoma of the cervix is causally linked to infection with specific oncogenic types of HPV, but not all infected women develop cancer. It has been suggested that injectable progestogen-only contraceptives (IPCs), combined estrogen–progestogen oral contraceptives (COCs), or both may act as cofactors with HPV, as a cause of cervical cancer. Evidence also suggests that IPCs may reduce the risk of cervical cancer. South Africa is an ideal country to test this hypothesis, because exposure to IPCs and COCs is common, as is invasive cervical cancer.

The University of Pretoria is one of the institutions participating in NCI clinical trials as part of the Eastern Cooperative Oncology Group.

Spain

Informal cooperation between NCI and scientists in Spain focuses (a) on signal transduction pathways activated by growth factors and their modification in human cancer; (b) on the evaluation of high-dose chemotherapy regimens followed by autologous bone marrow transplantation as therapy for patients with acute lymphoblastic leukemia or malignant lymphomas; and (c) on the elucidation of the cell biology of Ewing's sarcoma and related primary tumors.

NCI is initiating collaborative studies with the Institut Municipal d'Investigacio Medica, Barcelona, to evaluate the role of occupational exposures and gene–environment interactions in the development of bladder cancer.

Sweden

NCI supports a research project of a U.S. investigator who is studying risk and prognostic factors for postpartum breast cancer, by using a database that links the Swedish Medical Birth Registry, National Cancer Registry, and Registry of Causes of Death. A term pregnancy may have opposing effects on breast cancer risk: an adverse effect shortly after delivery and a beneficial long-term effect. The patients in this study are more than 5,000 women who had one or more childbirths between 1973 and 1992 and who had a breast cancer diagnosis during the same period.

Investigators in an NCI-supported project at the Karolinska Institute, Stockholm, are studying the role of genital HPV as a cause of carcinoma in situ of the cervix. Although a causal role of HPV is likely, no large population-based, prospective study has examined (a) the role of HPV in the natural history from normal epithelium to carcinoma in situ; (b) the role of cell-mediated immunity, as determined by human leukocyte antigen haplotype, microheterogeneity, or mutations in the HPV genome; or (c) the role of other factors that may determine transience or persistence of HPV infection. Nor has the purported orderly progression or monoclonal origin of cervical neoplasia been established. The Swedish investigators are conducting an interdisciplinary case–control study, nested in a population-based cohort. NCI also supports research at the Karolinska Institute that is directed toward understanding how polymorphisms in the estrogen receptor gene may affect the risk of breast cancer and endometrial cancer.

At Uppsala University, NCI supports epidemiologic studies of the risk of second primary lung cancer due to radiation and chemotherapy for breast cancer or Hodgkin's disease.

Tanzania

A series of tumor tissue blocks has been collected at medical facilities in Kenya and Tanzania, to characterize the association between Hodgkin's disease and Epstein-Barr virus (EBV). The data are consistent with other reported findings and suggest that, in the two locales evaluated, childhood Hodgkin's disease may be causally associated with EBV. To complete this comparative study, tissue samples from patients with Hodgkin's disease have also been obtained from various ethnic groups identified in the Singapore cancer registry. Evaluation of these additional cases will establish the causal relationship between EBV and Hodgkin's disease in these different geographic locales.

Burkitt's lymphoma has been associated with EBV and malaria, and tissue samples consistently have the c-*myc* translocation. This translocation was shown to be absent from a series of specimens from patients from Tanzania whose disease was diagnosed in the 1970s. To validate these findings, new specimens were collected for evaluation. Confirmation of these findings would suggest an alternative mechanism in the pathogenesis of Burkitt's lymphoma. Samples obtained will be used to evaluate possible genetic susceptibility to Burkitt's lymphoma.

Trinidad and Tobago

NCI investigators working with the Caribbean Epidemiology Center, Trinidad and Tobago, are continuing studies on the prevalence of HTLV-I and HIV infection in the healthy population in Trinidad and Tobago. The purposes of the research are (a) to systematically obtain samples and data on lymphoreticular malignant disease, (b) to develop and follow cohorts at high risk for HIV (e.g., homosexual men and male and female prostitutes), and (c) to evaluate risk factors related to viral infection and disease outcome, with particular emphasis on interaction of HTLV-I and HIV.

NCI collaboration with the University of the West Indies, St. Augustine, involves a series of epidemiologic, clinical, and experimental studies to define the distribution and determinants of HTLV infection and the possible role of HTLV as a cause of cancer. An important future direction is to perform follow-up studies on infection in patients with HTLV and HIV and to use these high-risk populations to define the natural history and pathogenesis of these viruses in terms of disease outcome.

Turkey

A hospital-based case–control study of several cancers is being conducted in collaboration with the Social Security Agency Hospital, Istanbul, to identify occupational causes of cancer in Turkey.

United Kingdom

Cooperation continues between NCI and British scientists, particularly in the field of radiotherapy. Clinical trials of fast-neutron therapy have long been supported at Clatterbridge Hospital, Merseyside, England; the University of California, Los Angeles; the M. D. Anderson Cancer Center, Houston, Texas; and the University of Washington, Seattle. These NCI-supported trials are the only ongoing phase III studies in the world that are designed to evaluate the use of neutrons in the treatment of cancers of the prostate, lung, and head and neck.

At the University of London, England, NCI supports studies on prediction of human tumor response by using magnetic resonance spectroscopy with ^{31}P.

NCI is collaborating with researchers at British Nuclear Fuels and Westlake Scientific Consulting, in the United Kingdom, to evaluate cytogenetic end points as biomarkers of occupational exposure to ionizing radiation in workers at the Sellafield nuclear reprocessing plant, Cumbria, England.

Vietnam

NCI supports studies investigating the efficacy of oophorectomy plus adjuvant therapy with tamoxifen in prevention of breast cancer recurrence in patients in Vietnam. The purpose of adjuvant tamoxifen therapy is to counteract the undesirable effects of oophorectomy on bone and the cardiovascular system.

Zambia

In collaboration with colleagues in Zambia, NCI scientists have analyzed tumor tissue from women with multiple tumors of nodular Kaposi's sarcoma. Methylation patterns of the androgen receptor gene (HUMARA) were evaluated for 31 tumors from eight patients. Most of the tumors in all eight patients had highly skewed methylation (i.e., predominant methylation of one HUMARA allele), and the same allele was methylated in all the tumors with skewed methylation. These data are inconsistent with results from independent clonal transformations. The findings indicate that Kaposi's sarcoma arises at multiple sites as a disseminated monoclonal tumor.

Taiwan

Information exchange continues between scientists in the United States and Taiwan on diseases endemic to that part of the world: hepatitis due to HBV, nasopharyngeal carcinoma, and T-cell leukemia.

Since 1989, NCI has collaborated with the National Taiwan University, Taipei, and the National Institute of Dental Research, NIH, on studies of genetic, viral, and environmental factors in the cause of nasopharyngeal carcinoma. This work includes a completed case–control study of nasopharyngeal carcinoma in Taipei and a new country-wide effort to enroll high-risk families in a study to investigate the role of inherited predisposition and environmental–genetic factors in this disease.

Multinational Studies

Second malignant neoplasms are being studied among 1-year survivors of testicular or ovarian cancer reported to population-based cancer registries in Canada, Denmark, Finland, the Netherlands, Sweden, and the United States. A cohort survey will characterize risk of a second cancer by age and time since treatment, and a nested case–control study is expected to evaluate and quantify leukemia risk associated with specific therapies. In a separate study, population-based cancer registries in these countries are being used to study second cancers in patients with Hodgkin's disease treated by radiation or other therapeutic regimens.

Cancer risk is being evaluated in a cohort of 20,000 patients who have received bone marrow transplantation for leukemia, aplastic anemia, or other diseases, from 1964 through 1992. Data are being obtained from the United States and from 234 transplant teams in more than 50 countries that report data to the International Bone Marrow Transplant Registry in Wisconsin. A cohort study has been conducted, and analyses are ongoing. A nested case–control study in this cohort is being performed to obtain information on treatment and cancer risk factors that are not available from the computerized files on the cohort.

Thyroid cancer data from 14 case–control studies conducted in Italy, Japan, Norway, Sweden, Switzerland, and the United States are being analyzed together to clarify associations between hormonal, medical, and environmental risk factors and thyroid cancer.

The NCI Registry of HIV-Infected Patients With Hemophilia contains data on cancer occurrence in patients at U.S. and foreign hemophilia treatment centers, including sites in Brazil, Canada, Germany, Israel, Spain, Sweden, and the United Kingdom.

Activities With International and Multinational Organizations

OIA is NCI's liaison with international agencies involved in cancer research and prevention. OIA also maintains connections with premier cancer centers worldwide and with organizations that have international components.

European Organization for Research and Treatment of Cancer

NCI's collaborative program with EORTC and with CRC in the United Kingdom remains highly successful in providing a regular flow of new compounds for NCI's automated assay for screening potential anticancer and anti-AIDS agents. The therapeutic potential of these agents is tested in a panel of in vitro human tumor cell lines. The collaborative program also provides new drugs for phase I and II clinical evaluations. Participating cancer centers include the following:

- the Jules Bordet Institute, Brussels, Belgium;
- the Finsen Institute, Copenhagen, Denmark;
- the Institute for Cancer Research, Sutton, Charing Cross Hospital, London, and Paterson Institute for Cancer Research, Manchester, England;
- Institut Gustave Roussy, Paris, France;
- the Immunology Research Group, Freiburg, the German Cancer Research Center, Heidelberg, and the Max-Delbruck Center for Molecular Medicine, Berlin, Germany;
- the National Institute of Oncology, Budapest, Hungary;
- the Mario Negri Institute for Pharmacological Research, Milan, Italy;
- the Daniel den Hood Cancer Center, Rotterdam, and Free University and A. van Leeuwenhoek Tumor Center, Amsterdam, the Netherlands;
- the Radium Hospital and Norsk Hydro's Institute for Cancer Research, Oslo, Norway;
- the University of Edinburgh and the University of Glasgow, Scotland; and
- the Swiss Cancer Center, Bellinzona.

EORTC joins some 2,000 European cancer specialists in 250 institutions into a single working team. The EORTC Data Center, Brussels, provides the statistical and data-processing services required for state-of-the-art clinical trials. EORTC provides NCI with early access to results from cancer research supported by the European Community.

International Agency for Research on Cancer

IARC, an organization in Lyon, France, that is affiliated with WHO, has 18 member states: Argentina, Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Norway, Russia, Sweden, Switzerland, the United Kingdom, and the United States. Among NCI-supported projects at IARC is the publication of a monograph series evaluating the carcinogenic risk of chemicals to humans. These *IARC Monographs* are used as authoritative sources of information by governments and regulatory bodies worldwide. NCI represents the United States on the Governing Council of IARC. The U.S. portion of IARC's regular budget is provided by the U.S. Department of State.

International Union Against Cancer

UICC, which is based in Geneva, Switzerland, is a worldwide organization with more than 250 members in 84 countries. NCI provides partial support to the UICC Committee for International Collaborative Activities, the UICC Detection and Diagnosis Program, and the UICC Fellowship and Personnel Exchange Program, which receives funding for International Cancer Technology Transfer fellowships. More than 100 short-term fellowship awards were made during FY 98.

Organization of European Cancer Institutes

The Organization of European Cancer Institutes was founded in 1978 to foster cooperation among cancer centers of the Economic Community and the Warsaw Pact countries. With the disintegration of the Warsaw Pact, interaction among cancer centers in the United States, Central and Eastern Europe, and Western Europe has improved greatly. OIA represents NCI at the annual general assembly meetings of the Organization of European Cancer Institutes.

Pan American Health Organization

PAHO has been the recipient of an OIA contract that contributes to the support of the Latin American Cancer Research Information Project. PAHO has also been involved in translation of an oncology textbook and an elementary school health curriculum. (See also the section on "Cancer Information Dissemination Projects.")

IX.

National Institute of Child Health and Human Development

INTRODUCTION

The National Institute of Child Health and Human Development (NICHD) focuses primarily on the reproductive, physiological, and behavioral processes that determine and promote the health of children, adults, and families. The Institute's programs are based on the concepts that adult health and well-being are largely determined by episodes early in life, that human development is continuous throughout life, and that reproductive processes and the management of fertility are major concerns to the individual and society. Medical rehabilitation has become an important research objective as the NICHD programs explore ways to restore the potential and functional capacities of individuals when disease, injury, or a chronic disorder intervenes in the developmental process.

Research at NICHD encompasses a unique and broad scope of laboratory, clinical, and epidemiologic studies. This research attracts international researchers to train in the NICHD laboratories and creates extensive opportunities for international collaboration. Many of the Institute's goals have global importance. These goals include

- developing and evaluating methods for the regulation of fertility and research on reproductive health;
- advancing biomedical knowledge of pregnancy, fetal development, and birth;
- developing strategies to prevent infant and child mortality;
- identifying and promoting the prerequisites of optimal physical, mental, and behavioral growth and development in infancy, childhood, and adolescence;
- contributing to prevention and amelioration of mental retardation and developmental disabilities; and
- advancing knowledge of the pathogenesis, epidemiology, and natural history of the human immunodeficiency virus (HIV) and related retroviruses in pregnant women, mothers, infants, children, and adolescents.

Much of NICHD's research relies on the disciplines of cellular, molecular, and developmental biology to elucidate the mechanisms and interactions that guide a single fertilized egg cell through its development into a multicellular, highly organized, adult organism. These interests involve research as varied as molecular neurophysiology and vaccine development. The Institute's research also includes performance of applied studies and support of biomaterials development, which together form the core of medical rehabilitation science.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

The largest, most comprehensive data analysis of its kind has found that pregnant women with HIV can reduce by about 50% the risk of transmitting the virus to their infants. This reduction in risk occurs if HIV-positive women decide to deliver by cesarean section before labor begins and before the membranes have ruptured. NICHD researchers analyzed data on 8,533 pairs of mothers and infants from 5 European and 10 North American studies of mother-to-infant HIV transmission. The analysis suggests a potential role for elective cesarean section as an additional intervention to decrease mother-to-infant HIV transmission, regardless of whether prophylaxis with zidovudine (AZT) is received.

An NICHD-supported investigator found that, since the 1970s, infant mortality increased by more than 20% in African cities with populations between 50,000 and 1 million, while it decreased 14% in rural areas. In cities of more than 1 million population in Latin America and sub-Saharan Africa, the rate of decline in infant mortality has slowed. Poor nutrition, high morbidity due to diarrhea, low school enrollment, and rapid population growth are limiting the pace of further declines. These results underscore the need to understand trends involving population growth and urbanization of developing societies and their effect on health and mortality.

Using data from a rural population in Uganda, a study funded by grants from NICHD and the National Institute of Allergy and Infectious Diseases (NIAID) provides evidence that HIV infection may lower fertility in women, both by decreasing the chances that conception will occur and by increasing rates of pregnancy loss. These findings suggest that reduced fertility among HIV-positive women could (a) result in reduced perinatal transmission of HIV; (b) produce lower estimates of HIV prevalence derived from monitoring of newborn infants; and (c) contribute to the spread of infection in societies in which failure to produce offspring may lead to dissolution of marriages and acquisition of new partners by HIV-infected women and their partners.

A new diphtheria–tetanus–acellular pertussis vaccine was approved for manufacture and use in the United States. NICHD intramural scientists developed this vaccine. It will be produced by North American Vaccine and marketed as Certiva. Extensive vaccine trials were conducted in the United States and Sweden.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

NICHD will participate in a major research project involving Canada, Mexico, and the United States. The study resulted from a meeting on reproductive health, in Mexico, in April 1998. Participants from the three nations agreed to undertake an observational study of preeclampsia, an important factor in maternal morbidity and mortality and a major determinant of preterm birth. Observational studies to evaluate early markers of preeclampsia will be conducted with 20,000 women in each of the three nations.

In a follow-up to the fiscal year 1997 (FY 97) bilateral agreement among the National Institutes of Health (NIH), the Indian Ministry of Health and Family Welfare, the Indian Council of Medical Research, and the Council of Scientific and Industrial Research, scientists from the United States and India met in New Delhi, in March 1998, for a scientific workshop and to develop a long-term bilateral program of research in reproductive and behavioral sciences. Guidelines for applications and review of proposals have been completed, and funding sources in both countries have been identified. The program has been widely publicized, and applications for research and training support are being reviewed. The Joint Working Group will meet annually to review activities and research plans to achieve the goals of improved contraceptive and reproductive health.

The program official of the NICHD Neonatal Research Network provided consultation on the creation of a Japanese Neonatal Research Network. The Japanese Ministry of Health has agreed to provide funding for 18 clinical centers, a statistician-epidemiologist, and technical assistance. Scheduled to start in April 1999, the first study launched through the new Japanese research network will be a trial of indomethacin for prevention of intraventricular hemorrhage and patent ductus arteriosus in preterm infants.

In cooperation with the Russian Ministry of Health, NICHD supported the Research Public Health Institute (MedSocEconomInform), Moscow, and the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, to carry out a program of regular publication of joint reports, vital statistics, and journal articles analyzing the rise in Russian mortality. NICHD also supported the preparation of an extensive report on maternal and child health in Russia, and NICHD scientists provided technical assistance to improve Russian health statistics.

NICHD, through the Division of Epidemiology, Statistics, and Research (DESPR), continues to collaborate with the Vietnamese National Institute of Hygiene and Epidemiology and the Vietnamese Ministry of Health on a large-scale trial of the effectiveness of a locally produced, inactivated cholera vaccine.

In collaboration with the National Public Health Institute of Finland, DESPR also is conducting two studies related to diabetes. The first study examines the relationship between diabetes-associated human leukocyte antigen (HLA) markers in women with diabetes and the risk of malformation in their offspring. This study focuses on the role of genetic factors in teratogenesis. Another study explores the relationship between HLA type in parents with diabetes and the risk of diabetes in their offspring. A child whose father has diabetes is almost twice as likely to develop the disease as is a child whose mother has diabetes. Observed and expected HLA types in these families will be studied further to determine whether certain high-risk HLA types are linked to the spontaneous abortion of fetuses of mothers with diabetes.

NICHD is supporting investigators in Argentina, Belgium, Italy, and Sweden who are involved in research to address fundamental issues of how young children develop mental concepts and acquire language. This basic research with children has far-reaching implications for theories of early linguistic and cognitive development and will serve as the basis for additional research on specific language impairments in children.

Activities With International and Multinational Organizations

International Skeletal Dysplasia Registry

The International Skeletal Dysplasia Registry continues to grow as a major source of clinical, radiographic, morphological, biochemical, and molecular materials for research on disorders of skeletal dysplasia. Funded as part of a program project at Cedars-Sinai Medical Center, Los Angeles, California, the registry's computerized database contains more than 7,900 documented cases of skeletal dysplasias. It also includes photographs and radiographs of patients, chondro-osseous tissue fixed for morphological and ultrastructural studies, frozen bone and cartilage, cultured cells (fibroblasts, chondrocytes, and lymphoblastoid cell lines), and DNA. The registry staff collects materials on patients with skeletal dysplasias, distributes samples to appropriate investigators, performs clinical research by using the registry's computer system and database, and provides diagnostic assistance to investigators throughout the world. During FY 98, staff conducted clinics in Argentina, France, Spain, and Uruguay. The registry is now on the World Wide Web (www.csmc.edu//genetics/skeldys).

Reproductive Sciences of the Americas Network

Initiated in 1995, the Reproductive Sciences of the Americas Network (RSANET) fosters research collaboration among the participating countries of Argentina, Brazil, Canada, Chile, Mexico, and the United States. NICHD, along with organizations in the private sector, supports and coordinates the network's efforts. Through its electronic newsletter and bulletin board, RSANET provides information on career and training opportunities, relevant scientific meetings, and availability of reagents. NICHD and RSANET sponsor the Americas Fellows Program, which currently supports three Latin American postdoctoral investigators for training with reproductive scientists in Canada and the United States.

The RSANET research training course on Frontiers in Reproductive Cellular and Molecular Concepts and Technologies, designed with NICHD guidance, receives multiyear funding from public–private partnerships involving U.S. foundations, NICHD, and international funding agencies. An international panel of scientists selected 16 participants from 10 countries for the inaugural course, which was held at the Marine Biological Laboratories, Woods Hole, Massachusetts, on May 26–July 5, 1998. The participating countries included Argentina, Australia, Canada, Chile, India, Japan, Mexico, Portugal, the United Kingdom, and the United States. In 1999, 16 scientists will be selected from among postdoctoral fellows and early-career or midcareer, independent investigators to attend the course at the Marine Biological Laboratories, on May 24–July 4, 1999. Internationally acknowledged scientists will provide training in strategies and state-of-the-art methods for use in cellular, immunologic, and molecular biological research for exploration of emerging issues in the reproductive sciences.

World Health Organization

NICHD's collaboration with the World Health Organization (WHO) in a 4-year clinical trial of a new prenatal care model is nearing completion. The model is based on scientifically proven interventions for conditions known to affect the health of both the mother and her child. In this model, prenatal care takes place over four visits during the pregnancy of low-risk mothers, rather than the traditional 12–14 visits. The emphasis in the revised model is (a) to recognize and diagnose conditions and complications of pregnancy that are known to affect the health of the mother, the fetus, or both, and (b) to intervene and treat conditions and complications that are identified. The randomized trial was conducted with about 25,000 pregnant women in four countries: Argentina, Cuba, Saudi Arabia, and Thailand.

In further collaboration with WHO and the U.S. Agency for International Development (USAID), NICHD also supports a population-based case–control study of vasectomy and prostate cancer in New Zealand. The goal of this research is to determine whether vasectomy affects the risk of prostate cancer, both overall and taking into account age at vasectomy, age at interview or diagnosis, time since vasectomy, ethnicity, and other demographic factors. The study design allows pooling of the data with data from a WHO multinational study on vasectomy and prostate cancer.

Working with the WHO Regional Office for Europe and various coordinating centers, NICHD's DESPR sponsors U.S. research as part of a WHO project on Health Behavior in School Children. The study addresses the hypothesis that U.S. youth may have adopted lifestyles that place them at greater risk for certain health problems than their counterparts in other nations. It evaluates causes of adolescent injury, violence, and related behaviors. NICHD collaborates with the Substance Abuse and Mental Health Services Administration to complete both preliminary and full surveys, as required for participation in the WHO project, which coordinates the quadrennial survey that compares health behavior in adolescents in 30 countries. Data from the 1996 preliminary survey are under analysis; NICHD completed and submitted the full 1998 survey to WHO.

DESPR also cosponsors the WHO International Collaborative Effort on Injury Statistics, which is coordinated by NCHS. A working group of representatives from 15 countries is seeking to improve the comparability and quality of international statistics on injury, to provide the data needed to better understand the causes of injury and the most effective means of injury prevention. U.S. and Canadian investigators in this WHO study are using survey results to enhance the *International Classification of Diseases,* 10th revision, for classification of injury by activity, mechanism, and location. A recent advance report, based on data from 11 countries, gave preliminary results on international differences in mortality rates related to injury and the effects of classification on determination of causes, intent, and age-specific mortality. U.S. mortality rates from injury were comparable to those in New Zealand and Norway; lower than those in Denmark and France; and higher than those in Israel, the Netherlands, and the United Kingdom.

NICHD also partially funds the Cochrane Collaboration on Reproductive Health, in which WHO participates. Under this collaboration, NICHD and WHO are planning a conference on Mechanisms of Endometrial Bleeding As Affected by Steroidal Contraceptives.

NICHD is developing a cooperative program with WHO and the United Nations Foundation, to support international research across a range of priorities for research on maternal and child health, with emphasis on the development and evaluation of interventions. This initiative would be funded over a period of 5 years by the foundation and NICHD. The Institute will provide expert assistance in designing and publicizing the program, reviewing and ranking applications, and overseeing the initiative.

A 3-year contract awarded by NICHD to WHO, to evaluate a new prenatal care system in cooperation with an Argentinean research center, will conclude in 1999. Another NICHD contract with WHO supports field trials of killed oral vaccine for cholera, in Vietnam. The field trials will be completed in 2000.

NICHD staff continues to serve on several WHO committees related to Human Reproduction Program policy coordination; epidemiology; fertility-regulating vaccines; diarrheal disease vaccines; and trials of a rhesus rotavirus vaccine in Venezuela and a CVD 103-HgR oral cholera vaccine in Indonesia.

NICHD provides consultants to WHO for the following purposes:

- to review translated epidemiology training documents;
- to serve on the WHO Task Force on Post-Ovulatory Methods for Fertility Control;
- to provide statistical expertise to the Data and Safety Monitoring Board of the WHO MultiCenter Randomized Trial of Misoprostal in the Management of the Third Stage of Labor;
- to collaborate with the Pan American Health Organization on maternal and child health issues and training; and
- to provide expert advice on WHO-sponsored vaccine trials, evaluation activities, and related questions on vaccines and epidemiology.

NICHD also serves as a WHO Collaborating Center for Clinical Evaluation of Vaccines in Developing Countries.

Extramural Programs

NICHD supports extramural research with international components through grants to foreign investigators and institutions, as well as grants and contracts to domestic universities, hospitals, research institutes, and other facilities. Selected NICHD-funded research activities are described here.

Africa

The Population Council in New York, New York, continues to examine the influence of preventive health care practices and community characteristics on child mortality. This research was prompted by evidence that child mortality has not decreased in several countries since the late 1970s, despite increasing immunization coverage, use of oral rehydration therapy, access to potable water, and female literacy. Results indicate that smaller-than-expected declines in infant and toddler mortality can be attributed largely to incomplete immunization in countries in sub-Saharan Africa. Community-level factors in rural areas (e.g., access to paved roads, distance to urban centers, and means of waste disposal) also affect child survival in countries with high mortality rates.

NICHD-supported researchers at the Population Council also work with investigators in Ghana to examine the impact of social marketing and dissemination of information on family planning and prevention of HIV and acquired immunodeficiency syndrome (AIDS) on the reproductive health behaviors of women in Ghana. In addition, researchers at the Population Council and the State University of New York, Stony Brook, are investigating the role of social dynamics of diffusion in the pace and timing of changes in fertility in Ghana. They are studying the process that underlies the adoption of modern contraceptive methods.

Another Population Council study investigates the quality of schooling for adolescents in Kenya and its effect on educational attainment and reproductive behavior. Using data from approximately 800 adolescents, their parents, principals, and teachers, the study explores the link between the quality of primary schools and attrition of female attendance. Families largely determine whether girls remain in school, but dropout rates are higher among girls whose teachers and schools discriminate against them. Other research in Kenya examines how schooling affects young girls' attitudes toward and adoption of reproductive health practices.

NICHD supports several studies in Africa that focus on HIV infection and disease in mothers and children. These include clinical trials (1) in Kenya to determine the effect of breast-feeding on the rate of HIV transmission from infected mothers to their offspring; (2) in Malawi to determine whether vitamin A reduces the rate of HIV transmission from infected mothers to their offspring; (3) in Tanzania to determine whether micronutrients given to mothers may reduce the rate of HIV transmission from mother to child; and (4) in Uganda to determine whether vitamin A lessens the severity of HIV-related disease in children with HIV.

In addition, NICHD funds studies (1) in Kenya to examine levels of HIV DNA and RNA in cervical and vaginal secretions during pregnancy and after delivery, to design interventions that might reduce the risk of HIV transmission from mother to infant; (2) in South Africa to investigate the role of T-cell reactivity in children exposed to HIV but not infected, in efforts to reduce the risk of subsequent HIV transmission through breast-feeding; and (3) in Uganda to analyze variation in HIV genotype, in efforts to determine the possible role of V3 loop variants that might increase the risk of HIV transmission from mother to infant.

In a couple-based study of family planning in four sub-Saharan countries with recent declines in fertility, a researcher at Johns Hopkins University, Baltimore, Maryland, expects that information obtained from husbands will significantly contribute to the prediction of contraceptive use.

Through an interagency agreement with NIAID, NICHD supports an epidemiologic study on the influence of oral and injectable contraceptives on the spread of HIV infection. The research is being conducted through the HIV Network (HIVNET) for Prevention Trials. In this case–control study, HIV-negative women are being monitored for HIV seroconversion at sites with a high incidence of HIV infection in South Africa, Thailand, Uganda, and Zambia.

Asia

Investigators from the East-West Center, Honolulu, Hawaii, and the University of Pennsylvania, Philadelphia, are examining whether women's empowerment leads to reduction in fertility. Results indicate that community values and nationality strongly predicted the economic decision-making power of married women in five countries in Asia: India, Malaysia, Pakistan, the Philippines, and Thailand. This finding persisted even when the investigators controlled for factors such as age, socioeconomic status, and land ownership.

Latin America

Researchers at the University of Pennsylvania, Philadelphia, are expanding the Mexican Migration Project database on populations migrating from Mexico to the United States, to include migratory populations from nations in the Caribbean, Central America, and South America. Questionnaires originally developed for use in Mexico are being modified and applied to representative samples of four communities each in Colombia, the Dominican Republic, El Salvador, Guatemala, Peru, and Puerto Rico. Community-level data, economic indicators, and oral histories will be added to the database and made available via the Internet through a Web site already established by the Mexican Migration Project, which will be renamed the Latin American Migration Project.

Argentina

In Buenos Aires, investigators at Maternidad Sarda are conducting a clinical trial, similar to the Management of Hyperbilirubinemia study in preterm infants in Greece. The trial will determine whether administration of a heme oxygenase inhibitor (tin mesoporphyrin) to term infants will reduce or eliminate the need for phototherapy and exchange transfusion. Enrollment of infants in the study is proceeding on schedule, and preliminary results are encouraging. The treatment appears efficacious, and no complications have occurred.

Bangladesh

Using data from the Matlab district in Bangladesh, which were collected by the International Center for Diarrhoeal Disease Research, Dacca, an investigator from the University of Pennsylvania, Philadelphia, is studying the role of social effects in individual decision making about contraceptive use. Social effects operating within narrow religious groups in individual villages were found to be an important predictor of this decision-making behavior.

Brazil

A researcher from the University of Texas, Austin, is investigating the extent to which women in Brazil use sterilization as their primary method of fertility control. Preliminary findings indicate a strong link between cesarean delivery and subsequent choice of sterilization. This study examines the determinants of that link, focusing on issues important to individual women and those important to the medical service delivery system where they deliver their children.

A project at the University of Michigan, Ann Arbor, is analyzing household responses to long- and short-term changes in household economic conditions in Brazil. The project addresses change in the educational attainment of children as a result of variations in participation in the labor force by women and children during an economically volatile period in Brazil (1976–1995). These data are being used to test whether worsening economic conditions in households contributed to a decline in children's schooling and advancement. An expanded theoretical model considers the effect of long-term economic status and of short-term economic shocks on the need for children to repeat school grades and on children's employment.

Scientists at the Rand Corporation, Santa Monica, California, are studying the consequences of rapid urbanization and environmental degradation on infant mortality in the Brazilian state of São Paulo over the past 25 years. The results of this research should help to foster policies that might mitigate the negative health effects of rapid urbanization, which is occurring at unprecedented rates around the globe.

Canada

An investigator from McMaster University, Hamilton, Ontario, is conducting a longitudinal study of motor function in children with cerebral palsy. The goal of the research is to create motor growth curves for cerebral palsy that are similar to those on the growth charts used to follow the height and weight of children as they mature.

NICHD continues to fund McMaster University for establishment of the Neonatal Collaborative Review Group (NCRG) within the International Cochrane Collaboration. NCRG develops and maintains a database for neonatal trials that produces systematic reviews of evidence on the effectiveness and safety of neonatal therapies. Members of the NCRG editorial board conduct reviewer training, assign volunteer reviewers, coordinate the peer review of meta-analyses and reviews, and publish a newsletter. International coordinators help to promote NCRG activities abroad. In FY 98, NCRG completed 41 reviews and 6 updates of reviews.

The Neonatal Inhaled Nitric Oxide Study Group (NINOS), a collaboration of the NICHD Neonatal Research Network and the Canadian Inhaled Nitric Oxide Study Group, is conducting a multicenter, international, randomized control trial of inhaled nitric oxide (INO) in the treatment of term or near-term infants with early hypoxic respiratory failure. This 2.5-year trial will enroll 400 infants and will be conducted at 14 U.S. network sites and 10 Canadian sites, with funding from the Neonatal Research Network and INO Therapeutics. This new INO trial follows the successful collaboration of the NINOS group on the first large trial of INO in the treatment of term neonates with respiratory failure, which was reported in the *New England Journal of Medicine* in 1997. The new study will be the key trial for a New Drug Application to the U.S. Food and Drug Administration.

Newly funded scientists are studying the influence of skeletal loading and calcium supplementation with dairy products on bone mineral accretion in a group of prepubertal Canadian children. The skeletal-loading intervention program includes a variety of skipping and box-jumping activities designed to stimulate bone formation. The groups receiving dietary intervention are given supplements of dairy products to attain a calcium intake of 1,200 mg/day.

An investigator at the Hospital for Sick Children, Toronto, Ontario, is examining the effects of stimulant medication (methylphenidate) on specific cognitive, particularly inhibitory, processes in children with attention-deficit hyperactivity disorder.

At the University of Colorado Health Sciences Center, Denver, researchers are continuing their studies of glutaric acidemia in a population of Island Lake Canadian Indians. This condition results from an inborn error of lysine and tryptophan oxidation, which causes degeneration of the basal ganglia and a progressive movement disorder in childhood.

Chile

Scientists at the University of Michigan, Ann Arbor, are testing the hypothesis that hypomyelination causes the changes in neuromaturation observed in iron-deficient anemic infants. They also are testing a model that explains why iron-deficiency anemia in infancy is associated with poorer developmental outcome. In view of the importance of iron in myelin formation and maintenance, impaired myelination is a promising explanation for recent evidence of immature neuromaturation in 6-month-old infants with iron-deficiency anemia. The model postulates that hypomyelination and impaired dopaminergic function contribute to altered behavior in anemic infants, which interferes with their learning from the physical and social environment and makes them more vulnerable to the effects of environmental stressors, leading to poor intellectual and motor development and more internalizing behaviors. Early iron-deficiency anemia affects 20%–25% of the world's infants and many poor or minority infants in the United States. This study provides a unique opportunity to examine biological and environmental effects on developmental outcome among poor children in a developing country. Because 86% of all children are born in developing countries, there is an urgent need to modify models based on industrial societies, to address conditions in developing countries.

China

Researchers from the University of North Carolina, Chapel Hill, collected and disseminated unique data sets from the longitudinal China Health and Nutrition Survey. The survey examines the effects of health, nutrition, and family-planning policies and programs implemented by national and local governments and how the social and economic transformation of Chinese society affects the health and nutritional status of China's population. These data sets contain information on health, nutritional and reproductive history, and the education and income of women and their children. Preliminary results from a study of access to health care suggest that China has achieved broad distribution of widely used clinics and other services at the local level.

A project at the State University of New York, Albany, explored the changing intergenerational relationships in Chinese families, including living arrangements, frequency of contact, exchanges of financial assistance, and mutual help. Evidence from a study of populations in two large cities in China shows persistence of a pattern of adult children residing with their parents, despite many changes in society. Reasons for this persistence include a deeply rooted history of coresidence across generations and a scarcity of housing.

An investigator from Queens College, New York, New York, continues to examine different forms of migration within China between 1982 and 1995, a period of rapid change and economic transformation. The investigator is measuring the effects of foreign investments, rural enterprise, and inequality in urban and rural income on migration patterns.

NICHD is supporting the first nationally representative survey of Chinese sexual health and family behavior. This is a timely study because China is experiencing sharp annual increases in incidence of AIDS and other sexually transmitted diseases. The investigator will describe the social organization of human sexuality in China and test whether social networks explain the pattern of spread of sexually transmitted diseases.

Investigators at the University of Michigan, Ann Arbor, are conducting a series of studies with children aged 2–4 years in China, to elucidate the links among concepts, language, and theory construction in early childhood. In another study, by scientists at Harvard University, Boston, Massachusetts, the effects of rotating shift work on adverse reproductive outcomes in China will be assessed. This prospective cohort study will enroll 1,150 women working in Chinese textile mills—700 workers on rotating shifts and 450 workers on a regular day shift. These women are married nonsmokers between the ages of 20 and 34 years who have permission to have a child and are attempting to become pregnant.

Costa Rica

Researchers at the Rand Corporation, Santa Monica, California, and the University of North Carolina, Chapel Hill, are analyzing the effects on age-specific mortality of a large expansion in government health insurance coverage in Costa Rica. Research suggests that lower health care costs lead to higher demand for health care, but little is known about the magnitude of overall changes in mortality as health insurance coverage increases in low-income populations.

Investigators at the University of Michigan, Ann Arbor, continue to examine the functional consequences of early iron-deficiency anemia. Preventing this condition in infancy may improve developmental outcome. Building on previous studies in Costa Rica and Guatemala, researchers observed that lower test scores persisted at 5 years of age, despite correction of anemia with iron therapy administered during infancy. Scientists are assessing the significance of these findings by performing follow-up on a group of 11- to 12-year-old Costa Rican children whose iron status and development were measured in infancy and at age 5 years. The study includes detailed tests of attention, because more problems in this area were reported at age 5 years for children who had anemia as infants. Behavioral measures also are being used to evaluate the hesitance, wariness, and internalizing problems noted at age 5 years in these children.

A critical element of this study is evaluation of cognitive and motor development during the transition to adolescence. To interpret the cognitive, motor, and behavioral results, scientists are assessing intervening and masking variables, such as the family's situation (e.g., household composition and type of employment). They also are collecting samples of serum prolactin and salivary and plasma cortisol, to determine neuroendocrine responses to stress.

The investigators are expanding this research to include a second interconnected study of the behavioral effects of iron-deficiency anemia in infancy. This project, modeled after research in malnutrition, will determine whether providing environmental stimulation in addition to iron therapy can correct the altered behavior and whether the intervention is more effective in the 1st or 2nd year of life. Behavior, development, and maturation of the nervous system will be compared before and after 6 and 12 months of intervention. Because approximately 25% of the world's infants experience iron-deficiency anemia, the observation of impaired functioning in school could benefit pediatric populations worldwide.

Denmark

The NICHD-funded investigators at Case Western Reserve University, Cleveland, Ohio, will use cytogenetic, molecular, and epidemiologic tools to investigate the hypothesis generated by their previous work on Down syndrome (trisomy 21). The primary goals of this revised program are to study the cause of trisomy 21, including the mechanisms of dysfunction and the factors that influence its frequency, and to investigate the phenotypic consequences of the extra chromosome 21.

Germany

A U.S. postdoctoral fellow at the European Molecular Biology Organization, Heidelberg, who is supported by an NICHD National Research Service Award, is studying the role of the Mad gene during retinal development in *Drosophila*. The research will determine the effects of constitutively activated Mad on retinal development; explain genetically the relationship between the Mad gene and "early eye genes"; and use genetic-screening techniques to identify genes that interact with the Mad gene in retinal development. This research should add substantially to understanding of transforming growth factor β signaling in mediation of eye development.

Greece

Since 1989, researchers from Rockefeller University, New York, New York, have carried out a clinical trial in Athens, to determine whether the administration of a heme oxygenase inhibitor (tin mesoporphyrin) to term infants would reduce or eliminate the need for phototherapy and exchange transfusion to treat hyperbilirubinemia. In a study of 844 preterm infants, the use of the inhibitor proved to be safe and efficacious. Current research activities in Greece are centered on the follow-up with infants at 3 and 18 months of age. Preliminary results reveal no deleterious side effects or sequelae attributable to this therapy.

Guatemala

A research project at Emory University, Atlanta, Georgia, is focusing on the causal relationships among malnutrition, infection, and diet in preschool children living in impoverished communities. The study tests several hypotheses. One hypothesis is that diet modifies the effect of infectious diseases on nutritional status; for example, diarrhea has a negative influence on the nutritional status of children with poor diets but little impact on the nutritional status of those with adequate diets. To test these hypotheses, scientists are comparing the results of standard epidemiologic approaches with those of alternative approaches, particularly structured equation modeling. Although such modeling is frequently used in the social sciences, its use in the biomedical field is rare. Comparing structured equation modeling with standard epidemiologic techniques will ascertain the usefulness of the modeling method in other areas of health research that involve multilevel determinants of reciprocal causal relationships. Each year, approximately 14 million children die, most from the synergistic effects of infection and malnutrition. In addition to the Guatemalan databases, large databases obtained in collaboration with the Save the Children Organization also will be used to examine the causes of child mortality. This research will enable policy makers to design effective interventions to improve global health and survival.

Other investigators at Emory University continue to study the effects of improved nutrition in early childhood on later functional performance in adolescents and adults. This research links two data sets originating from a landmark longitudinal study of growth and development, which was conducted in 1969–1977 in four Guatemalan villages. Scientists have collected additional data on reproductive history and have assessed long-term effects of a nutritional intervention that was shown to improve growth and development in the preschool period. This follow-up analysis indicates that nutritional interventions in pregnancy and early childhood culminate in improved body size and intellectual performance.

These Emory University researchers recently initiated another follow-up project in Guatemala that evaluates the generational effects of malnutrition. Scientists are studying the effects of nutritional insults during growth and development on the subsequent reproductive behavior of women and the growth of their offspring. These efforts link mothers and children of the original study, who are now grandmothers and mothers, with the current generation of children. The research focuses on the hypothesis that malnutrition and developmental impairment in early childhood constrain the future capacity of women to bear healthy newborns and their ability to care for them and, thus, constrain the growth and development of the next generation. Data are being collected on maternal body composition, lactational performance, birth weight and newborn status, physical growth and maturation, child health and nutrition, cognitive assessments in adults and children, maternal–child behaviors, and aspects of socioeducation. This study promises to be the most comprehensive current evaluation of the repercussions of malnutrition in early childhood across generations and the first such investigation in a developing country.

India

Using data from a longitudinal study of households in rural India between 1968 and 1982, a researcher at the University of Pennsylvania, Philadelphia, has confirmed that when there is greater technological change in a region, the residents at each level of education earn a higher salary, the effect of schooling is amplified, and private investment in schooling is greater. In a study of 4,000 households in 250 villages in India, researchers are examining the effect of economic growth and population size on environmental changes. The goal of the project is to provide information on interventions that could alter the environmental impact of population growth on forest degradation.

Investigators at Johns Hopkins University, Baltimore, Maryland, continue to evaluate the role of zinc in childhood growth and development and the effects of zinc deficiency on childhood morbidity. They are developing a new method to analyze longitudinal data acquired during randomized, controlled field trials of dietary supplementation that involve variables of childhood growth and development. This research builds on the recent discovery that zinc replacement lessens the effects of childhood diarrhea, as established in a field trial in India.

These scientists also are analyzing data from two large studies on zinc supplementation targeting outcomes such as infectious diseases, morbidity, growth, and development. A comparison of new and traditional methods will help to determine the best approach for studying hypotheses on the potential effect of zinc supplementation. The two studies will increase understanding of the role of zinc deficiency in childhood illness, which is particularly important to specific high-risk groups. Investigators expect to establish nutritional guidelines for zinc fortification of foods in developing countries. Recent results reveal that zinc supplementation reduces the incidence of pneumonia and augments cellular immunity. These results are important for much of the developing world, where pneumonia is a major killer in children younger than 5 years of age. The findings suggest that improving zinc intake will improve the health and survival of children in developing countries. This research also is relevant to the United States, because recent studies have shown that approximately 30% of U.S. children are not obtaining sufficient zinc from their diet.

Indonesia

Investigators at the Rand Corporation, Santa Monica, California, are conducting the Indonesian Family Life Survey of Mothers and Children. This survey will produce a major new panel of data to support research on the health and well-being of women and children in a low-income setting. On the basis of current data, one researcher has examined the role of women's empowerment within the household in outcomes related to reproductive health. Measures of a woman's empowerment, such as her share of assets within the household and her resources relative to those of her spouse, were related to whether the woman received prenatal care.

Other Rand Corporation studies in Indonesia are examining governmental funding of family planning and how it affects both women's fertility and their economic opportunities. Investigators also are studying the effects of the community and the family on child health in Indonesia, by using a data set that contains 16 years of information collected from households, community facilities, and five censuses of village infrastructure. Preliminary findings indicate that better-educated mothers are more likely to identify specific health problems and to access prenatal care early in pregnancy. Other analyses on the effect of access to health care show that introducing a maternity clinic in a village decreases the odds of infant mortality by almost 16%, whereas an additional physician reduces the odds by only about 1.7%.

Israel

At Boston University, Massachusetts, a researcher is examining the effect of immigration from the Soviet Union between 1990 and 1994 on Israel's labor market. Soviet immigration increased the size of Israel's labor force by 10%. The main goals of this study are to learn about the process of assimilation into new labor markets and to investigate the role of wages (a) on accumulation of human capital, including language and training and (b) on the search for employment. These factors are being studied in immigrants to Israel and in a sample of native Israelis.

Italy

A project at the University of Colorado, Denver, involves clinical studies of normal pregnancies and pregnancies complicated by fetal growth restriction. The studies focus on (1) use of new fetal surveillance techniques to improve classification of the clinical severity of fetal growth restriction and (2) use of stable isotope methods to monitor amino acid transport and metabolism, based on observations that fetal amino acid concentrations are significantly reduced in pregnancies resulting in fetal growth restriction.

Jamaica

At Baylor College of Medicine, Houston, Texas, scientists are testing the hypothesis that reduction in plasma nutrient transport proteins, which is induced by infection in malnourished patients, results from the compromised synthesis of these proteins, secondary to a decrease in aromatic amino acids and cysteine availability. A specific hypothesis is that the shortage of aromatic amino acids is due to an infection-induced stress response, which increases synthesis of other proteins (e.g., acute-phase proteins and glutathione). In baseline studies in 22 severely malnourished Jamaican children with or without infections, fibrinogen synthesis did not increase in response to the stress of an infection. This finding may explain why recovery from injury and surgery is delayed in malnourished individuals.

Infections also play a role in mediating the lower plasma concentrations of transport proteins in malnourished patients. The concentration of plasma apolipoprotein A-1 is partly determined by in utero growth, and this relationship may contribute to the increased risk of coronary heart disease in adults who had low birth weight. This study will enhance understanding of the pathogenesis of reduced plasma nutrient transport proteins and protein metabolism in malnourished individuals with an infection. The findings are expected to suggest therapeutic approaches to stimulate protein synthesis during early treatment, restore concentrations of nutrient transport proteins, and limit whole-body protein catabolism.

Japan

Investigators at Duke University, Durham, North Carolina, are working to isolate genes involved in autistic disorder. The gene search will focus on chromosome 15q11–q13, because of recent evidence that links this region to this condition. The primary aim of the project is to produce a detailed genetic map of this region in families with members who have autistic disorder, to determine the most likely locus of the gene for this condition. DNA from families in Finland and Japan also will be examined for methylation abnormalities and chromosomal duplications, insertions, deletions, or inversions.

Malaysia

Researchers from the Rand Corporation, Santa Monica, California, are examining retrospective data collected in the first and second Malaysia Family Life Survey, to study migration patterns in a poor but rapidly developing economy. The study will focus on the effect of life-cycle events such as marriage and education in individuals, the extended family, and the community, as well as other characteristics that might explain migration behavior.

Mexico

At Brown University, Providence, Rhode Island, researchers are analyzing the effect of local economic conditions in Mexico on migration within Mexico and migration to the United States. They are using retrospective life histories and cross-sectional data available from the Mexican Migration Project, based at the University of Pennsylvania, Philadelphia, and from the Zacatecas Migration Survey.

In the largest field study of Mexican migration, investigators from the University of Pennsylvania used a combination of survey and ethnographic techniques to collect data on Mexican migrants in the United States and western Mexico. Analyses of these data helped to determine the factors that encourage migration to the United States and those that influence return migration. Investigators highlighted three fundamental forces at work: social networks of family and friends already living in the United States; an increasing level of knowledge and experience about the United States by Mexican workers; and increasing linkages between the economies of Mexico and the United States.

Investigators at Eastern Virginia Medical School and Medical College, Norfolk, performed follow-up on a cohort of Mexican mothers to ascertain whether human milk prevents disease in breast-fed babies. The study demonstrated a dramatic increase in exclusive breast-feeding in mothers receiving home visits from a trained peer counselor. Researchers also are assessing the variability of concentrations of antibody, glycoconjugates, and anti-inflammatory components in the milk of lactating women. They are evaluating genetic control as a determinant of the concentrations of protective factors in maternal milk.

These scientists continue to determine the effectiveness of feeding specific purified glycoconjugates identified in human milk, for prevention of diarrhea due to specific enteropathogens. They will determine the efficacy of maternal immunization given to boost concentrations of antibodies in breast milk for prevention of diarrhea in breast-fed infants. This project will define the relevant antibodies and glycoconjugates that protect infants from rotavirus diarrhea. The overall goal is to prevent infection and illness despite viral antigenic diversity. Investigators are working to prove that antibodies and nonantibody factors in human milk bind viral pathogens and protect breast-fed infants from disease. They have found that human milk provides antibodies and nonantibody factors that may explain why breast-feeding appears to protect infants from symptomatic shigellosis.

Investigators at Eastern Virginia Medical School and Medical College also are conducting field studies in San Pedro Martir, Mexico City, a predominantly low-income urban area with a population of 45,000. Community-based studies have been conducted in this area for 18 years. These investigators recently conducted a blinded, controlled, community-based clinical study to evaluate the effect of feeding a probiotic mixture containing *Lactobacillus acidophilus, Bifidobacterium infantis,* and *Lactobacillus reuteri* on prevention of community-acquired diarrhea among children 12–36 months of age. After random assignment of the type of feeding, 120 control children received their usual feeding and 123 children received the beverage containing the probiotic mixture for 14 weeks. A significantly higher proportion of children who were fed the probiotic mixture were free of diarrhea (76%), compared with the proportion of children in the control group who were free of diarrhea (64%). Seven cases of rotavirus diarrhea occurred among control children, and two cases occurred among the children receiving the probiotic mixture. Although not statistically significant, this trend suggests that probiotics may protect against rotavirus diarrhea.

Another field project, in Mexico and Norfolk, involved the immunization of postpartum women with tetravalent rhesus rotavirus vaccine. Researchers are evaluating the safety and immunogenicity of the vaccine and the effect on concentrations of antibodies and lactadherin in human milk after administration of the vaccine. The vaccine was given to 30 women in Mexico and 30 in Norfolk within 24 hours or at 14 days after delivery. To date, 60 women have enrolled and are progressing through the 4-month study.

Nepal

An investigator from Pennsylvania State University, University Park, is expanding an ongoing project in Nepal. This research provides an opportunity to observe how population, institutional, and environmental changes interrelate in a relatively pristine environment that is just beginning economic development.

A new project at the University of Michigan, Ann Arbor, will investigate the influence of changing social contexts on marriage, childbearing, and contraceptive use on a sample of 150 neighborhoods in Nepal's Chitwan Valley. The same investigator will examine the relationship between changes in population processes and the environment, by using a graphical information system.

New Zealand

Scientists at the University of Auckland are studying the molecular basis for the biological activities of human lactoferrin; addressing wider questions of iron homeostasis by extending these structure–function studies to serum transferrin; and evaluating the structural basis of specificity in these proteins. This research will elucidate the control of levels of iron and other trace elements in bodily fluids, which is related to diseases of iron overload or deficiency and bodily defense mechanisms, especially antibacterial and antioxidant activity. Aspects of the biology of human milk and infant health and the bioavailability of trace elements will also be explored. This research is an extension of previous crystallographic studies of lactoferrin and newly developed structural work on transferrin. During the course of the research, the scientists initiated (a) a new program of complementary techniques in x-ray crystallographic studies of human transferrin and (b) investigation of the ability of lactoferrin to bind certain antitumor complexes. In addition, further advances were made in relation to the nature of conformational change in lactoferrin and the versatility of metal and anion binding.

At Pennsylvania State University, University Park, researchers are conducting a cross-generational, longitudinal study of child-rearing practices of mothers and fathers of 3-year-olds, in Dunedin, New Zealand. By studying 500 parents from a cohort of approximately 1,000 New Zealanders born in Dunedin two decades ago, the study will determine whether earlier family influences are predictive of parenting during adulthood and whether a supportive marital experience disrupts the intergenerational transmission of problematic parenting. Insight into these issues will help to prevent problematic parenting and promote competent parenting.

Peru

Investigators at the University of Alabama, Birmingham, are conducting a study in Peru to determine whether breast-feeding during pregnancy is associated with a change in the composition of early milk and a subsequent decrease in milk volume during the next lactation. A cohort of 168 multiparous women will be enrolled. One-half of the cohort will be women who breast-fed during the third trimester of pregnancy, and one-half will be women who have not breast-fed past the 1st month of pregnancy. These women will be identified after delivery and will be matched for interbirth interval and sex of the newborn. Preliminary results suggest that breast-feeding during pregnancy changes the composition of colostrum. A decrease in mature milk production may lead to early introduction of feeding bottles, thereby increasing infant morbidity, poor growth, and mortality. This research promises to yield new information on the biological consequences of lactation during pregnancy, which will increase understanding of the health implications of this widespread practice.

Russia

The Russian Longitudinal Monitoring Survey was designed as a household-based survey to monitor the effects of Russian reforms on the well-being of households and individuals. The survey measures the impact of these reforms on consumption of goods, nutritional status, and patterns of use of health care services. Analyses of the data by investigators from the University of North Carolina, Chapel Hill, indicate that Russia's older adults have not experienced a major decline in economic or nutritional well-being during the reform period. In fact, obesity appears to be a much more serious health problem than chronic malnutrition in older adults. The data also show much higher rates of alcohol intake since the reforms have been in place, with higher alcohol intake in older adults who are heavy drinkers of alcohol.

NICHD consulted with NCHS on the Vital and Health Statistics report, *Maternal and Child Health Statistics: Russian Federation and United States, Selected Years 1985–95,* which was published in the spring of 1998. NICHD and NCHS are jointly supporting activities to improve the Russian infrastructure to obtain reliable vital statistics and health indicators. Staff at NICHD and NCHS continue to support efforts to achieve this goal. Pilot studies in three regions of Russia involve training in the use of revised birth and death certificates. Also, computer-assisted training in the use of the *International Classification of Diseases,* 10th revision, will be implemented for Russian states.

Rwanda

Researchers at Johns Hopkins University, Baltimore, Maryland, are investigating whether vitamin A supplementation can enhance immunity and reduce morbidity and mortality for children infected with human immunodeficiency virus type 1 (HIV-1) in Rwanda.

Saudi Arabia

The Baylor Child Health Research Center, Baylor College of Medicine, Houston, Texas, recently was awarded new project development funds to support gene-mapping studies and cloning strategies in primary congenital glaucoma (PCG). Investigators screened 25 Saudi Arabian families with PCG and identified three missense mutations in 24 of these families. The most common mutation changes a glycine to a glutamic acid in 78% of the PCG chromosomes. The second mutation changes an arginine to a tryptophan in 10% of the PCG chromosomes. The third mutation changes an aspartic acid to an asparagine in 6% of the PCG chromosomes. Detailed clinical and molecular examinations of the mildly affected patients and their environmental exposures are expected to identify additional factors that influence the expression of the PCG phenotype. Such knowledge will suggest pharmacological targets for the antenatal moderation or postnatal therapy for PCG and possibly other forms of glaucoma. Future research will increase understanding of the embryology of ocular development and the role of other drug-metabolizing enzymes in organogenesis.

Sweden

A cross-linguistic, cross-sectional, longitudinal study of infants and toddlers who are learning to speak English or Swedish examines the relationships among articulation-based phonetic aspects of child speech, the acquisition of language-specific phonological features, and the use of phonemic contrast in learning to talk. Investigators from the University of Seattle, Washington, are tracing the development of particular consonant and vowel phones that occur in both English and Swedish. Findings will lead to a more complete understanding of the process of phonological acquisition in the young child and will serve as the basis for additional studies of children with phonological disorders.

Thailand

A group of investigators from the University of North Carolina, Chapel Hill, is studying contraceptive use in a rural area of Thailand. The investigators are drawing on a mix of qualitative and quantitative data to explain patterns of contraceptive use within and between villages. Preliminary findings indicate that different contraceptive methods tend to predominate in different villages. The researchers propose that these patterns may result from a feedback mechanism whereby use of a method within a village stimulates use by others because of the information shared by villagers.

NICHD also supports a study in Thailand to determine whether shortened courses of AZT given to HIV-infected pregnant women might reduce the rate of mother-to-fetus HIV transmission. Another NICHD study is exploring the epidemiologic, immunologic, and virological characteristics of HIV-infected Thai women and the role of protective immunity in the transmission of HIV infection from mother to infant. The University of Chiang Mai is one of the sites for the NICHD-supported study of HIV infection and use of contraceptive hormones, which is conducted by the HIVNET project in Africa. (See also the section on "Africa.")

A newly funded NICHD project, with an investigator from the University of Michigan, Ann Arbor, will provide a comprehensive empirical assessment of problems that AIDS poses for the elderly in Thailand. The investigator will determine the magnitude of the problem among older persons affected by AIDS and examine the effect on adult children and grandchildren.

Uganda

At Pennsylvania State University, University Park, a researcher is using epidemiologic network modeling and social network data in Uganda to examine the issues related to concurrent and sequential partnering and the impact of sexual networks on transmission of HIV infection. The data obtained from field studies on the sexual network in Uganda will be compared with data from similar studies in Thailand.

United Kingdom

Investigators at the University of London, England, are examining the relationships among children's social and moral understanding, family and peer relationships, and school adjustment during the period of middle childhood. This sample of children of African-Caribbean descent in England has had follow-up from age 4 years. The current funding extends the study until the children are 9 or 10 years old and includes a cross-section of children identified as "hard to manage" and at risk for later problems with conduct and peer relationships.

A project at Johns Hopkins University, Baltimore, Maryland, is studying the effects of divorce on the mental health of persons aged 7–33 years. The analysis indicates that factors present before the marriage dissolved contribute to the effect of parental divorce on adults. In addition, findings suggest that parental divorce and its aftermath affect the mental health of adults. Moreover, a parental divorce during childhood or adolescence appears to continue to have a negative effect, even when the child or adolescent reaches ages in the 20s or 30s.

A multisite NICHD Collaborative Program of Excellence in Autism is part of the International Autism Genetics Consortium. This Program involves researchers from Yale University, New Haven, Connecticut; the University of Chicago, Illinois; and the University of California, Los Angeles. The international team includes NICHD-funded scientists from the United States; Oxford University and the University of London, England; and universities in Denmark, France, Germany, Greece, and the Netherlands. The team has completed a genome scan based on 97 autistic sibling pairs who were uniformly characterized.

Researchers in London, England, are investigating the effect of specific forms of mother–infant relationships in the first 24 months of life on infant social, emotional, and cognitive development. They are comparing attachment patterns in infants of mothers with borderline personality disorder and infants of mothers with no psychiatric diagnosis. In addition, a 3-year NICHD-funded project at the University of London will build on earlier molecular genetic analyses related to cognitive ability in children. Researchers will conduct the first systematic genome scan for allelic association, by using a new DNA-pooling technique developed as part of the study. The results will contribute to the understanding of neurophysiological pathways between genes and cognitive development.

Zambia

In a newly funded project, an investigator will use a randomized design to compare contraceptive use and pregnancy incidence in a group of couples in Zambia who are given education on and access to contraceptives and in a group of couples who receive the same education and access, plus a motivational message. Another study focuses on sexual networks as a method to identify effective and efficient intervention strategies for prevention of the spread of HIV and other sexually transmitted diseases. A significant proportion of adults older than age 30 years had at least one concurrent partnership among their last three sexual partnerships. These concurrent partnerships, rather than the actual number of partnerships, may account for the rapid and pervasive spread of HIV in the study population.

International Meetings

During FY 98, NICHD researchers attended, made presentations at, and helped to convene many international conferences, seminars, and workshops. Selected meetings that involved NICHD participation, are as follows:

- Symposium on Historic Reflections, Current Developments, and Unresolved Issues in Maternal and Fetal Medicine, in Montevideo, Uruguay, on March 2–4, 1998;
- 5th SIDS (sudden infant death syndrome) International Conference, in Rouen, France, on April 20–23, 1998;
- 3rd International Symposium on Diabetes and Pregnancy, in Rome, Italy, on April 27–29, 1998;
- 4th World Conference on Injury Prevention and Control, in Amsterdam, the Netherlands, in May 1998;
- International Collaborative Effort on Injury Statistics Working Group, in Amsterdam, in May 1998;
- Nobel Forum on Fetal Medicine, at Karolinska Institute, Stockholm, Sweden, on May 28–29, 1998;
- Joint meeting of the European Society for Developmental Pharmacology and NICHD, in Corsica, Italy, on June 4–6, 1998;
- International Congress on Recent Advances in Perinatal Medicine, sponsored by the 2nd Institute of Obstetrics and Gynecology, in Erice, Italy, on July 3–7, 1998;
- International Congress on Pediatrics, in Amsterdam, on August 9–14, 1998;
- Japan Society of Pharmacology and Therapeutics, in Tokyo, Japan, on September 10–12, 1998; and
- Colloquium on Perinatal Endocrinology, in Nancy, France, on September 20–22, 1998.

Intramural Programs and Activities

Many international researchers are given the opportunity to train and work with NICHD scientists on projects conducted in the Institute's laboratories. NICHD intramural scientists also are involved in collaborative efforts with investigators in many countries.

Division of Epidemiology, Statistics, and Prevention Research

The Office of the Director, DESPR, collaborates with investigators of the Aga Khan University, Karachi, Pakistan, on studies of maternal and infant mortality and related outcomes, such as preterm births and intrauterine growth retardation (IUGR). IUGR is present in about 24.4% of live births in certain parts of Karachi. Risk factors include low level of maternal education, paternal unemployment, consanguinity, short interval of birth to conception, short maternal stature, and low maternal weight. Interventions emphasizing family planning and programs aimed at improving nutrition and education for women of childbearing age are expected to have a major impact on achieving this goal. An intervention to integrate existing components of prenatal and delivery care is planned for a suitable site in Baluchistan.

In the Collaborative Perinatal Project with Denmark and Sweden, which is part of a study on low birth weight across generations, the Office of the Division Director is analyzing data from girls who were born in the 1960s. The investigators have interviewed girls who were small for gestational age or preterm at birth and control girls. Hospital records of their deliveries have been retrieved.

The Epidemiology Branch participates in the WHO study of Health Behavior in School Children and cosponsors the International Collaborative Effort on Injury Statistics. (See also the section on "Activities With International and Multinational Organizations.")

The Branch continues to study markers for fetal alcohol syndrome with the University of Chile, Santiago. Researchers are identifying pregnant women with high alcohol intake, collecting blood specimens over the course of the pregnancy, and examining the ability of various markers to predict which offspring will have fetal alcohol syndrome.

In collaboration with the U.S. Naval Medical Research Unit 3 and the University of Alexandria, Egypt, the Branch continues (a) to evaluate the role of enterotoxigenic *Escherichia coli* (ETEC), rotaviruses, and astroviruses as causes of diarrhea in a cohort of infants and (b) to conduct phase II trials of an inactivated oral ETEC vaccine in differing age strata of this population. Researchers at the field site in Egypt are preparing to study the epidemiology of *Helicobacter pylori* infections in a cohort of newborn infants and to conduct a large-scale, phase III, efficacy trial of the ETEC vaccine. The Branch, together with scientists in India, is studying the epidemiology of *Salmonella typhi* infections and is evaluating differences between active and passive surveillance in determining disease burden.

A field site for evaluating enteric fever vaccines has been established in South Vietnam. A baseline epidemiologic study of enteric fever was conducted in three communes, and safety and immunogenicity studies of enteric vaccines were completed in preparation for a phase III trial. An exploratory surveillance of shigellosis is being conducted in North Vietnam for evaluation of *Shigella* vaccines.

In collaboration with the Health Research Board of Ireland and Trinity College, Dublin, the Branch continues to study the cause of neural tube defects. This research focuses on genetic errors that result in mutants of the enzymes involved in folate metabolism. Specifically, a gene defect produces a thermolabile variant of the 5,10-methylene tetrahydrofolate reductase enzyme. The original study, which was recently expanded, confirmed that the mutant enzyme is found significantly more frequently in individuals with neural tube defects than in healthy individuals. A recent published report indicates that, in women who received 200 mg of folic acid per day, folate in red blood cells was raised to levels that are known to protect against most neural tube defects in infants and that 100 mg is also protective in many women.

Laboratory of Molecular Genetics

The Laboratory of Molecular Genetics is broadly concerned with gene structure, expression, and transmission, especially as concomitants of development. Techniques include molecular biology, genetics, transgenic models, histochemistry and cytochemistry, and embryological manipulations. Many model systems are under study, including viruses, bacteria, flies, zebra fish, and frogs. Numerous scientists from foreign countries are among the Laboratory's researchers at the postdoctoral and senior levels. During FY 98, the Laboratory included among its staff, researchers from China, France, Germany, Hungary, India, Ireland, Israel, Italy, Japan, Korea, Russia, and the United Kingdom. The Laboratory has ongoing collaborations with scientists in Germany, Israel, and Japan on a variety of projects. Members of the Laboratory participated in international conferences and visited institutes in various countries, including Austria, Canada, France, Germany, Israel, Japan, and the United Kingdom. Laboratory scientists act as members of advisory committees to institutions such as the National Science Foundation of Austria.

Developmental Endocrinology Branch

The Developmental Endocrinology Branch conducts basic and clinical investigations of endocrine diseases, with broad emphasis on adult, pediatric, and reproductive endocrinology. Much of the Branch's research aims to discover the molecular causes and cures of reproductive, growth, and developmental disorders. International scientists have important roles in this research program, which involves both basic and clinical studies. Visiting Fellows and Visiting Scientists from many countries participate in research meetings, clinical conferences, medical rounds, and outpatient clinics. During FY 98, the Branch had 30 visitors from Argentina, Australia, Belgium, Brazil, China, Germany, Greece, Hungary, India, Japan, Lebanon, New Zealand, Nigeria, the Philippines, Poland, Turkey, and the United Kingdom. The Branch has established ongoing collaborative efforts with the Bulgarian Academy of Sciences; the University of Toronto, Ontario; the Institute of Maternal and Child Research, University of Chile, Santiago; the United Medical and Dental School, University of London, England; Medizinische Universitätsklinik, Würzburg, Germany; the University of Athens Medical School, Greece; and Tel Aviv University, Israel.

Laboratory of Cellular and Molecular Biophysics

The Laboratory of Cellular and Molecular Biophysics studies biological phenomena such as membrane fusion, intracellular interactions, metabolic analysis and mass spectrometry, and macromolecular analysis, to elucidate their physical basis. Physical and organic chemists, membrane biochemists, cell biologists, and physicians interact to extend understanding of physiological and pathophysiological mechanisms, often using the language of mathematics and theoretical physics. This Laboratory develops and uses novel, noninvasive technologies to probe physical parameters of living systems ranging from cells to humans. At the same time, the Laboratory's investigators synthesize and study systems of well-defined molecular composition and structure that exhibit an essential biological function. This approach provides a robust description of the physicochemical basis of molecular and physiological activity. Scientists from Belarus, Canada, China, France, Israel, Russia, Spain, and the United Kingdom all work in an extremely interactive laboratory.

Laboratory of Comparative Ethology

The Laboratory of Comparative Ethology collaborates on several long-term studies with research teams from 15 countries in Africa, Asia, the Caribbean, Central and South America, and Europe. One collaborative study examines the relationship between patterns of mother–infant interaction and the emergence of language and cognitive competence over the 1st 4 years of life in children in Argentina, Belgium, France, Israel, Italy, Japan, Kenya, and the United Kingdom. A follow-up study of the same children at 10 years of age is in the planning stage. A second series of studies focuses on the effects of various day-care arrangements on the social, emotional, and cognitive development of infants, toddlers, and grade school children in Germany and Sweden. A third major collaboration, involving Israeli researchers, investigates factors that influence children's eyewitness testimony and recall memory for specific events. Collaborating scientists from Canada, the Central African Republic, Colombia, and Germany are assessing the values and practices of parents in diverse cultures. Finally, several foreign investigators are collaborating with scientists in the Laboratory of Comparative Ethology in the study of various aspects of biobehavioral development in four nonhuman primate species living in natural habitats in Brazil, Costa Rica, and Puerto Rico and in a nature preserve in southern Germany.

Heritable Disorders Branch

The Heritable Disorders Branch trains foreign scientists and supports extensive collaborative research efforts. Current Branch associations include joint studies with scientists from Belgium, Canada, Denmark, France, Germany, India, Israel, Italy, Japan, Sweden, and the United Kingdom.

A Visiting Fellow from Australia is developing a gene therapy approach to correcting osteogenesis imperfecta, by using ribosome technology. Visiting Fellows from Canada and Japan are collaborating on the cloning and expression of the glucose-6-phosphate transporter gene. Visiting Fellows from India are working to characterize newly uncovered human uridine diphosphate (UDP)-glucuronosyltransferases; are isolating the cDNA (complementary DNA) and the gene for pancreatic soluble phospholipase A_2 uteroglobin receptor cDNA and performing gene cloning and signal transduction; and are characterizing the gene for acid ceramidase and performing mutation analyses in patients with Farber's lipogranulomatosis. A Visiting Fellow from Israel is studying cystinosis gene mutations and intracellular trafficking of the CTNS gene product. Three Visiting Fellows from Italy are working, respectively, on gene therapy for glycogen storage disease, by using mice deficient in glucose-6-phosphatase; on generating a knock-in nonlethal murine model for osteogenesis imperfecta; and on characterizing genetically defective bilirubin UDP-glucuronosyltransferase from patients with Crigler-Najjar syndrome. Visiting Fellows from the Netherlands and Thailand are collaborating to study cystinosis and Hermansky-Pudlak syndrome gene mutations and the functions of the gene products. A Visiting Fellow from Turkey is examining expression of SREBP in fibroblasts of patients with Smith-Magenis syndrome.

Collaboration includes studies with Belgian scientists on gene mutations in sialuria; with Danish researchers on cystinosis gene mutations; with British investigators on UDP-glucuronosyltransferase; and with Israeli researchers on glycogen storage disease. The Branch's bone researchers are collaborating with Canadian scientists studying bone morphometrics and Italian scientists engaged in studies of binding between mutant collagen and other proteins. The phospholipid group collaborates with French colleagues on hereditary IgA (immunoglobulin A) nephropathy; with German scientists on familial Fn glomerulopathy; and with scientists in India on the uteroglobin receptor.

Laboratory of Developmental and Molecular Immunity

The Laboratory of Developmental and Molecular Immunity conducts clinical studies ranging from phase I evaluations to efficacy trials of the Laboratory's investigational vaccines. These include acellular pertussis vaccines and their derivatives, as well as enteric bacterial disease vaccines. Studies are ongoing in Israel, the United States, and Vietnam and are being considered for Kenya and Myanmar.

The Laboratory has hosted Visiting Scientists and Guest Researchers from China, the Czech Republic, Ghana, Mexico, and Slovakia. The investigators are working to characterize bacterial pathogenesis and immunity, examining the structural and functional roles of the major histocompatibility antigens, and investigating the mechanisms regulating immune response at the cellular level. These activities have led to presentations of data at international meetings in Chile, Denmark, Italy, Japan, the Netherlands, Spain, Sweden, and the United Kingdom. The findings have also been published in several foreign-language research reports.

Active involvement of the Laboratory staff in vaccine development and field trials has led to several international joint studies. For example, the Laboratory collaborates with the Israeli Armed Forces in testing the efficacy of two types of *Shigella* conjugate vaccines (*S. flexneri* and *S. sonnei*) in adult volunteers. The University of Chile, Santiago, and the Laboratory are studying the *S. flexneri* conjugate and the *S. sonnei* conjugate in infants and school-age children.

The Laboratory and investigators in Iceland are studying non–species-specific protective antigens of pneumococcus that could assist in inducing vaccine immunity to the acute respiratory diseases of infants and children and of immunocompromised adults.

Endocrinology and Reproduction Research Branch

The Endocrinology and Reproduction Research Branch investigates basic aspects of hormone action in endocrine and reproductive tissues, with particular emphasis on peptide hormone receptors and their signal transduction mechanisms. The Branch maintains collaborative research programs with scientists in Germany, Hungary, Italy, and Japan and currently trains Visiting Fellows and Visiting Scientists from Argentina, Bulgaria, Canada, China, Croatia, Hungary, Italy, Japan, Korea, Mexico, Serbia-Montenegro, and Spain. During 1998, Branch investigators attended international conferences and symposia in Austria, Canada, Germany, Hungary, Italy, and Mexico and helped to organize international meetings in Budapest, Hungary, and Bethesda, Maryland.

Research Fellows from China, Japan, Korea, and Mexico are studying the structure–function properties and expression of receptors for angiotensin II, gonadotropin-releasing hormone (GnRH), prolactin, and luteinizing hormone, and the properties of angiotensin II and prolactin receptor subtypes. Investigators from Canada, Croatia, and Serbia-Montenegro are using single-cell imaging and electrophysiological techniques to study the regulation of cytosolic calcium oscillations and secretion in cells of the hypothalamus and the pituitary gland. Scientists from Argentina and Serbia-Montenegro are using cultured and immortalized hypothalamic neurons for in vitro studies on the control of GnRH secretion by neurotransmitters and other ligands. In a recently formed Unit on Molecular Signal Transduction, Postdoctoral Fellows from Bulgaria, China, and Hungary are investigating the role of inositol phospholipids and lipid kinases in cellular regulation and are using novel fluorescent molecular probes to image inositol lipid dynamics in single living cells.

Branch scientists recently initiated a study with the Peking Union Medical College, Beijing, China, to study the regulation of a DNA-binding protein by protein kinase C. In an effort to define the role of neurogranin in neural function, the Branch also has established a collaboration with scientists at the Leibniz Institut für Neurobiologie, Magdeburg, Germany, to study changes in neuronal plasticity in neurogranin gene knockout mice. Other Branch researchers are collaborating with investigators at the Department of Obstetrics and Gynecology, Lübeck, Germany, to study the manner in which gonadal steroids influence calcium signaling and gonadotropin secretory responses to GnRH and endothelin. Research with investigators at the University of Rome (La Sapienza), Italy, is focusing on aspects of communication among testicular compartments, the role of corticotropin-releasing factor and opiates in the modulation of testicular function, and the actions of growth hormone–releasing hormone in the testis and ovary. In addition, joint research on the role of endothelin in the intracellular signaling and growth regulation of ovarian tumor cells is being performed with investigators at the Regina Elena Cancer Institute, Rome.

Cell Biology and Metabolism Branch

The Cell Biology and Metabolism Branch carries out research in various areas of molecular cell biology. These areas include mechanisms of intracellular protein trafficking; the biology of intracellular organelles; T-cell activation; the characterization of tumor-suppressor genes and their products; genetic response to environmental stress; iron metabolism in humans; regulation of gene expression at the transcriptional and post-transcriptional levels; and developmental control of the cell cycle. The Branch is involved in an international effort in South Africa, Swaziland, and Zimbabwe to identify the genetics of iron overload in Africans. In addition, the Branch has other collaborative projects with groups in Canada, Germany, Israel, Italy, Japan, Korea, the Netherlands, and Switzerland. Among the scientists working in the Branch are researchers from Argentina, Canada, China, Estonia, France, Germany, India, Israel, Japan, the Netherlands, Turkey, and the United Kingdom. During FY 98, scientists from the Branch attended meetings in Austria, Canada, France, Germany, Ireland, Italy, Japan, Korea, Thailand, and the United Kingdom.

Laboratory of Mammalian Genes and Development

The Laboratory of Mammalian Genes and Development uses advanced gene targeting and transgenic technologies to study genes that control specific stages of mouse development. Of particular interest to the Laboratory are the development of the central and peripheral nervous systems and of pituitary and thymus glands, as well as mechanisms of genomic imprinting. The discovery and characterization of genes that control the development of these various tissues have resulted in the generation of mouse models of a variety of human genetic disorders. Among the scientists working at the

Laboratory are many from foreign countries, including China, Hungary, India, Israel, Italy, Japan, and Sweden. During FY 98, members of the Laboratory attended conferences and visited research institutions in Canada, France, Germany, and Israel. International research projects involve scientists in France, Germany, Israel, Japan, and Sweden.

Laboratory of Molecular Growth Regulation

The Laboratory of Molecular Growth Regulation conducts research in several complementary areas. One area of strong interest is molecular mechanisms underlying the control of mammalian cell proliferation. Scientists from Bulgaria, China, and Korea have contributed to studies on cellular protooncogenesis, tumor-suppressor genes, and chromatin-modifying genes, which are at the core of this part of the research program. A second major research focus within the Laboratory is regulation of gene expression, which is divided into three groups. One group, including scientists from China and Japan, investigates transcriptional initiation and termination of the gene for RNA polymerase III, as well as RNA processing and RNA–protein interactions. A second group, comprising scientists from Bulgaria, China, Japan, and Russia, focuses on interactions between transcription factors and the RNA polymerase II basal transcription apparatus. A third group, including scientists from China, France, India, Italy, Japan, and Korea, examines molecular mechanisms regulating the immune response. An additional independent group with internationally recognized expertise in eukaryotic DNA replication benefits from the contributions of scientists from China and Japan.

Laboratory of Developmental Neurobiology

The Laboratory of Developmental Neurobiology studies regulation of gene expression at the cellular and molecular levels and the physiological processes important for development of the nervous system. Of particular significance are the mechanisms that couple electrical and agonist-induced activity in neurons to regulatory phenomena. Extensive collaboration continues with scientists from Israel under a U.S.-Israel Binational Science Foundation Research grant. Research projects with scientists at the Chinese Academy of Science, Shanghai, are part of a program in which a Laboratory scientist serves as codirector of the Laboratory of Molecular Neurobiology there. Other interactions include work with scientists from the Czech Republic, Denmark, France, Norway, Spain, Sweden, Switzerland, the United Kingdom, and Venezuela. Guest Workers and Visiting Fellows working in the Laboratory are from Canada, China, Costa Rica, Denmark, Ethiopia, France, Iran, Japan, Korea, Malawi, and Spain. A member of the Laboratory serves on an advisory committee in Puerto Rico. Members of the Laboratory have organized and participated in a number of international meetings, including a novel Gordon Conference, in Beijing, China. A substantial Cooperative Research and Development Agreement (CRADA) is in place between the Laboratory and a French pharmaceutical firm.

Laboratories of the Scientific Director

In the Laboratories of the Scientific Director, the Section on Growth Factors is hosting one scientist from China and three from Japan. These investigators are studying various aspects of the action of nerve growth factor and other neurotrophins. One focus of the work involves the kinase that appears to mediate the cytoplasmic and nuclear actions of the factor. The investigators also are exploring the molecular changes that lead to the various phenotypic alterations induced by the factor in its target cells. In ongoing joint projects, two senior scientists from Israel are studying the role of ganglioside in the actions of nerve growth factor and the mechanism of the downregulation of mitogen receptors during nerve growth factor–induced differentiation. Collaborative efforts with two former postdoctoral students in Japan focus on the action of ganglioside in receptor function and on the kinase phosphorylating transcription factors that mediate the actions of nerve growth factor. During FY 98, members of the Section were involved in experiments with scientists from Israel and Japan.

The Section on DNA Replication, Repair, and Mutagenesis is interested in elucidating (a) the mechanisms for repair of exogenous damage to DNA, such as that caused by prolonged exposure to sunlight, and (b) the consequences of the damage if it is left unrepaired. The primary focus of these studies is the bacterium *E. coli*, but scientists in the Section are also investigating related processes in another bacterium, *Bacillus subtilis;* in a lower eukaryote, *Saccharomyces cerevisiae;* in a vertebrate, *Xenopus lavies;* and in mammalian cells (in mice and humans). The Section is led by a British Senior Investigator and includes three Visiting Fellows from France; one Visiting Fellow from Russia; and one from Spain. These studies also involve scientists from Japan and the United Kingdom.

Laboratory of Molecular Embryology

The Laboratory of Molecular Embryology researches the molecular mechanisms that establish and maintain stable states of gene activity during development. Particular interests include the significance of nucleic acid packaging for the function of the molecular machines that use DNA or RNA as a template.

Within the Laboratory, a British scientist supported by the Wellcome Trust investigates the role of DNA methylation in regulating transcription of the human fragile X mental retardation gene 1 promoter. The International Human Frontiers Research Program supports the research of German and Greek scientists on how the post-translational modification of chromosomal proteins influences gene expression. Japanese scientists supported by the Japanese Society for the Promotion of Science study the remodeling of somatic nuclei after transplantation into eggs. This process is important to understanding the molecular basis of recent successful cloning experiments. The Netherlands Natural Sciences Research Council supports a Dutch scientist in his studies of the role of DNA methylation in vertebrate development. Two Spanish scientists supported by the Spanish Ministry of Education and the Natural Sciences and Engineering Research Council of Canada are investigating the role of CCG triplet repeats in chromosomal structure and human disease.

The Laboratory of Molecular Embryology works with laboratories in China, France, Germany, Japan, Russia, Switzerland, and the United Kingdom. Principal investigators in the Laboratory have organized international meetings in Canada, China, Spain, and the United Kingdom. Within the Laboratory, scientists from Bulgaria, Canada, China, France, Germany, Greece, Japan, the Netherlands, Russia, South Africa, Spain, and the United Kingdom, together with colleagues from the United States, conduct independent research on gene expression.

Laboratory of Cellular and Molecular Neurophysiology

Scientists in the Laboratory of Cellular and Molecular Neurophysiology study signaling mechanisms in the central nervous system. In the Section on Neurophysiology and Biophysics, Visiting Fellows from China, Russia, Ukraine, and the United Kingdom are studying glutamate receptor channels, by using the techniques of biophysics and molecular biology. Current projects focus on mutational analysis of the pore region and polyamine block of kainate receptors; ion channel block by cytoplasmic polyamines; the mechanism of action of insect venom toxins on mammalian glutamate receptors; allosteric regulation of glutamate receptor desensitization; and assembly of kainate receptors.

In the Section on Molecular Neurobiology of Glia, Visiting Fellows from China, Italy, Singapore, and the United Kingdom are studying transcriptional regulation of glutamate receptor genes; regulation of glial development by neurotransmitters; signal transduction pathways and gene transcription in glia; and the role of voltage- and ligand-gated channels in the regulation of glial development in vitro and in vivo. In 1998, a senior scientist from Italy spent his sabbatical with the group. In the Unit on Cellular and Synaptic Physiology, Postdoctoral Fellows from Hungary and Italy are working on the analysis of synaptic transmission and plasticity in inhibitory interneurons in hippocampal brain slices; the expression of potassium channel subunits; and the physiological consequences of selective knockout of channel subunits in hippocampal neurons. A long-term collaborative effort has been established with a laboratory in Budapest, Hungary, to study the ultrastructure of neurons analyzed in electrophysiological experiments performed at the NIH.

In the Section on Neuronal Secretory Systems, Postdoctoral Fellows from Brazil and Japan work on the cell biology of Ca^{2+} wave propagation in different types of glial cells, by using optical recording techniques. A Japan Society Fellow has studied pineal cell excitability. The Section exchanges reagents with laboratories in Europe and Japan.

Members of the Laboratory were invited speakers at international meetings in Canada, the Czech Republic, and Greece, and staff from the Laboratory served as site visitors for review of the Wellcome Laboratory of Molecular Pharmacology in the United Kingdom.

Laboratory of Eukaryotic Gene Regulation

The Laboratory of Eukaryotic Gene Regulation uses a combination of genetics, molecular biology, and biochemistry to study mechanisms of translational and transcriptional control of gene expression and the structure and function of the general factors involved in the initiation steps of both processes in the yeast *Saccharomyces cerevisiae*. In addition, the mechanism of transposition by retrotransposon elements is being analyzed in the yeast *Schizosaccharomyces pombe*. Among the scientists working on these projects are Visiting Fellows and Guest Researchers from China, Germany, India, Japan, Korea, Spain, the United Kingdom, and Vietnam. In addition, collaborative research is conducted with laboratories in Japan and Spain.

Perinatology Research Branch

The Perinatology Research Branch carries out clinical and basic science studies of maternal, fetal, and neonatal disorders. Studies emphasize frequent, important, and clinically relevant human disorders, such as premature labor, congenital anomalies, IUGR, and pregnancy-induced hypertension. The Branch uses state-of-the-art imaging modalities to study fetal anatomy and hemodynamics, as well as invasive procedures of prenatal diagnosis (amniocentesis and fetal blood sampling) to study fetal physiology and disease. The Perinatology Research Branch continues its efforts to better understand the role of subclinical intrauterine infection as a cause of premature birth and long-term developmental handicap. The Branch pioneered fetal endoscopic surgery for the treatment of disorders of multiple gestation and congenital anomalies. The Perinatology Research Branch has Visiting Scientists and Postdoctoral Fellows from Australia, Israel, and Peru. Strong collaborative efforts have been established with the Department of Obstetrics and Gynecology, Catholic University, Santiago, Chile; Ben Gurion University, Israel; and the Department of Obstetrics and Gynecology, University of Seoul, Korea.

Laboratory of Integrative and Medical Biophysics

The Laboratory of Integrative and Medical Biophysics is dedicated to understanding the basic biophysical mechanisms underlying cell and tissue function. Many of the Laboratory's research activities involve applying physical and engineering sciences to the development of novel methods for determining cell and tissue status. A joint workshop on this subject was held on the NIH campus, Bethesda, Maryland. A large group of Japanese visitors participated in the workshop. In addition, Laboratory personnel have active, ongoing collaborations with scientists in France, Israel, Russia, and the United Kingdom on problems relating to optical imaging and the use of light for quantitative detection of fluorescent targets in tissue. Other collaborations, with Israeli and Italian scientists, aim to develop new techniques for characterizing tissue microstructure. These activities continue to result in joint publications.

The Laboratory has developed a novel technique, laser capture microdissection, for isolating pure subpopulations of cells from complex tissues and analyzing patterns of their gene expression. During FY 98, groups from Europe and Japan were introduced to this technique, and more than 40 instruments based on NIH design were placed in research laboratories in those countries. A number of foreign visitors presented seminars to members of the Laboratory and other investigators. One seminar, on biophysical modeling of cell locomotion, stimulated a possible long-term collaboration with a mathematical biologist from Germany. A member of the Laboratory and a colleague from the Technion University, Israel, jointly published a research report on the microstructural basis of cartilage mechanics and pathology.

Laboratory of Physical and Structural Biology

The Laboratory of Physical and Structural Biology focuses on the organizing powers of intermolecular and intramolecular forces of large molecules. It maintains close working ties with laboratories in several countries, most extensively Armenia, Brazil, Canada, China, France, Germany, Italy, Russia, Slovenia, Spain, and the United Kingdom. During FY 98, members of the Laboratory lectured in several European countries, including France, Poland, and the United Kingdom.

In collaboration with a German scientist, one Laboratory investigator developed a theory of interactions between various types of helical biomolecules. This theory explained the mechanisms of such phenomena as DNA overwinding from 10.6 base pairs per turn in solution to 10.0 base pairs per turn in fibers; spontaneous aggregation of DNA in the presence of certain ions; and B-to-A and packing transitions in dense DNA fibers. This work is building theoretical foundations for design of future experiments and for understanding forces that have already been directly measured among DNA double helices, four-stranded guanosine helices, collagen, and some polysaccharides.

A Visiting Fellow from Russia has conducted a series of experiments clarifying the role of dielectric reorganization of surface water in catalytic activity of enzymes. The measurements revealed that the reorganization energy is strongly reduced by solutes capable of disrupting the hydrogen-bond network structure. This reduction correlates with the change in the activation energies of hydrolysis by chymotrypsin and trypsin in the same mixed solvents. The latter findings explain how cosolvents may accelerate enzyme catalysis without directly interacting with the protein.

Research in interaction, stability, and phase transitions in lipid systems involved studies with scientists from Canada and Israel. The Laboratory continues study of intermolecular interactions in collaboration with KFA Research Center in Germany. Work with a Spanish scientist from the University of Castellón involved studies of mobile charge distribution in the vicinity of lipid planar bilayer, by using a small cation-selective channel gramicidin A. To understand the influence of membrane surface charge on ion channel function, scientists examined channel conductance when the surface charge density was varied, by using two techniques—titration of the lipid charge through bulk solution pH and dilution of a charged lipid by a neutral lipid. A previously unrecognized approach, the technique of dividing surface construction for the countercharged layer, describes the data well and, consequently, can be a useful analytic tool in membrane biophysics.

Visiting Scientists from Germany and Slovenia performed several studies on the arrangement of DNA and other long molecules at the high concentrations seen within viruses. The Laboratory also is working with scientists from Canada and France on phase transitions in lipid systems. In joint research with a French industrial laboratory (Rhodia), Laboratory scientists are determining the properties of polysaccharides for both biological function and potential application. In FY 98, members of the Laboratory participated in international conferences in France, Italy, Poland, Sweden, Switzerland, and the United Kingdom.

X.

National Institute on Deafness and Other Communication Disorders

INTRODUCTION

The National Institute on Deafness and Other Communication Disorders (NIDCD) conducts and supports research on the normal and disordered processes of hearing, balance, smell, taste, voice, speech, and language. NIDCD uses a wide range of mechanisms to achieve its mission in biomedical and behavioral research and in research training. NIDCD scientists, research grant programs, individual and institutional research training awards, career development awards, center grants, and contracts to public and private research institutions are used to accomplish the Institute's research goals.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

The NIDCD Division of Intramural Research continues to support an international consortium with the purpose of expediting the discovery of genes responsible for hereditary hearing impairment.

The consortium encompasses research on

1. Waardenburg syndrome, which is characterized by sensory hearing impairment, dystopia canthorum (wide distance between the inner corners of the eyes), pigmentary disturbances, and heterochromia irides (eyes of a different color);
2. Usher syndrome, which is distinguished by profound hearing impairment, vestibular areflexia, and retinitis pigmentosa; and
3. forms of hereditary hearing impairment.

Members of the consortium have published the sequence of a novel unconventional myosin type VIIA gene that causes Usher syndrome type 1b, the form responsible for most cases of Usher syndrome type 1. Mutations in this gene are also associated with dominant and recessive nonsyndromic hearing impairment.

Scientists from countries including Belgium, Colombia, Finland, France, Germany, Israel, Japan, Norway, South Africa, and the United Kingdom, as well as scientists throughout the United States, continue their efforts to map the genes responsible for syndromic and nonsyndromic hereditary hearing impairment. Almost 40 genes on as many different chromosomes have been identified for recessive and dominant nonsyndromic hereditary hearing impairment in families from Colombia, India, Indonesia, Israel, Lebanon, Newfoundland, Pakistan, Tunisia, and the United States, including Puerto Rico. The collaborative efforts fostered by the consortium have been instrumental (a) in identifying a large number of the genes responsible for hereditary hearing impairment and (b) in advancing the understanding of these disorders.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

The Laboratory of Molecular Genetics, Division of Intramural Research, has clinical protocols in place to study the genetics of hereditary hearing impairment in isolated populations throughout the world. NIDCD scientists are collaborating with other U.S. and international scientists to identify such populations and to map the genes associated with hereditary hearing impairment.

The Director of the Division of Intramural Research is the co–principal investigator for a binational grant for the United States and Israel to study properties of G protein–coupled receptors expressed in *Xenopus* oocytes.

The NIDCD Epidemiology, Statistics, and Data System Branch supports a research contract for a study entitled Genetic and Environmental Study of Hearing Loss in Nord-Tröndelag County, Norway. Using a population-based cohort of adults aged 20 years or older, the investigators are studying prevalence and genetic and environmental risk factors for age-related hearing loss and other hearing disorders, including tinnitus. Hearing is assessed directly with pure-tone audiometry and exposure to noise, and the presence of other conditions is ascertained through questionnaires.

The Branch also supports an interagency agreement with the National Institute of Child Health and Human Development for a study of hearing in children participating in the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC, or Children of the 90s). The children being examined are 5 years old and belong to a subsample of about 1,500 children in the Children in Focus study. In this project, longitudinal measurements of hearing will be correlated; most of these children were examined by "play" audiometry at the age of 2½ years. The children also have detailed longitudinal assessments for the presence of otitis media, based on tympanometry and health history.

In a study entitled Sensorineural Hearing Loss in Children, the Epidemiology, Statistics and Data System Branch supports the collection of data from a hearing examination of schoolchildren in Costa Rica. This is the first comprehensive epidemiologic study to assess the prevalence of sensorineural hearing loss in children in a Latin American country.

Findings from the Costa Rican Childhood Hearing Examination Survey for this study were presented at the Annual Meeting of the American Speech-Language-Hearing Association. Before this survey, preliminary estimates of the prevalence of sensorineural hearing loss in Costa Rica were about one-half the prevalence obtained from epidemiologic studies in Canada, the United States, and Western Europe. Because very few prevalence studies of hearing impairment conducted in developing countries have been epidemiologically sound, this was an ambitious collaborative study designed by demographers and statisticians at the University of Costa Rica, San José, together with an otolaryngologist and advisor to the Health

Ministry and a U.S. audiologist. The Epidemiology, Statistics, and Data System Branch provided partial funding for the investigation; developed a form for inquiring about the genetic background of children with sensorineural hearing loss; and participated in editing and review of the data set. The Hearing Research Institute of the Medical Research Council in the United Kingdom also provided partial funding for this study and, in particular, supplied a database program for computerized entry of study results.

Activities With International and Multinational Organizations

NIDCD continues to support and participate in two international research consortia to expedite the discovery of genes responsible for hereditary hearing impairment. This research is described in the section on "Highlights of Recent Scientific Advances Resulting From International Activities."

Extramural Programs

Canada

NIDCD continues to support research at the University of Saskatchewan, Saskatoon, on the glial cell modulation of axonal growth. The long-term goal of this research is to determine whether manipulation of the glial cell environment enhances or impedes the growth of olfactory and nonolfactory axons in the adult mammalian central nervous system.

Israel

NIDCD supports ongoing research at the Weizmann Institute of Sciences, Rehovot, on the identification, isolation, and molecular cloning of olfactory proteins, with particular emphasis on the components related to the previously unexplored area of regulation and termination of olfactory signals. The sense of smell plays an important role in vertebrate behavior. It is crucial for assessment of food quality, avoidance of harmful substances, and social interactions. In combination with parallel research, in which individual genetic differences in the human olfactory receptor repertoire are being investigated, the results of this work may shed light on the mechanisms underlying human olfactory sensory deficits.

International Meetings

NIDCD staff participated in various capacities at international meetings during fiscal year 1998. These included the following:

- presenter at the 6th Vienna International Workshop on Functional Electrostimulation, in Vienna, Austria;
- attendee at the 4th International Conference on Functional Mapping of the Human Brain, in Montreal, Quebec;
- presenter at the 5th SIDS (sudden infant death syndrome) International Conference and participant in the epidemiology committee meeting of the SIDS Global Strategy Update, in Rouen, France;
- presenter at the lecture on Organization of Glutamate Receptors in Neurons, at the Max Planck Institute for Experimental Medicine, Frankfurt, Germany;
- attendee at the International Mammalian Genome Conference, in Frankfurt, Garmisch-Partenkirchen, Germany;
- consultant on the U.S.-India Gene Mapping Project, in New Delhi, India, and Lahore, Pakistan;
- attendee at the European Consensus Development Conference on Neonatal Hearing Screening, in Milan, Italy;
- attendee at the BAMS (Basic Applied Myology Society) 1998 International Conference on Muscle Plasticity, in Abano Terme, Padua, Italy;
- attendee at the 13th Meeting of the European Chemoreception Research Organization, in Sienna, Italy;
- presenter on Advances in Head and Neck Tumor Immunology, in Sienna, Italy;
- attendee at the meeting of the Waardenburg Syndrome Consortium, in Cape Town, South Africa; and
- participant and consultant on The Prevention of Noise Induced Hearing Loss, at the World Health Organization, in Geneva, Switzerland.

Intramural Programs and Activities

There is a regular exchange of training opportunities between NIDCD and foreign countries. Visiting Scientists, Visiting Associates, and Guest Researchers from a number of countries are making significant contributions to the research efforts of the Division of Intramural Research. In particular, scientists from institutions collaborating with the Laboratory of Molecular Genetics have been trained in molecular genetic techniques at NIDCD laboratories. Individuals trained have come from Colombia, India, Indonesia, and Pakistan.

XI.

National Institute of Dental Research

INTRODUCTION

The National Institute of Dental Research (NIDR) is the lead agency for dental, oral, and craniofacial research in the United States. The Institute also promotes and supports research internationally. Increasingly, biomedical and behavioral research are recognized as global investments for solving health and disease problems. During the past year, international health has become a priority area for the National Institutes of Health (NIH). NIDR shares in this emphasis and is targeting selected research areas that can be enhanced by international collaboration. Already, scientists from the United States and other countries have combined their talents in many ways to advance understanding and prevention and treatment of dental, oral, and craniofacial diseases.

Throughout the past 50 years, collaborative international research has been an essential part of NIDR programs and activities. As NIDR celebrated its 50th birthday in fiscal year 1998 (FY 98), these global connections were recognized by the international science community. At the annual meeting of the International Association for Dental Research (IADR), in Nice, France, in June 1998, celebratory symposia were held to honor NIDR, along with the World Health Organization (WHO), which also was celebrating its 50th birthday. During the opening ceremonies of the meeting, the incoming president of IADR spoke of NIDR's increasing involvement in international research on oral health and specifically recognized the Institute's new Office of International Health (OIH) as evidence of NIDR's expanded interest in the international arena.

NIDR established OIH within the Office of the Director in March 1998. OIH, which coordinates NIDR's worldwide programs and activities, is directed by the Associate Director for International Health, who previously guided NIDR's international activities while also serving as Director, Division of Extramural Research. Now a separate office, OIH has a larger mandate. Its main functions are

- to serve as liaison with international agencies and foreign organizations;
- to coordinate dental, oral, and craniofacial research activities under agreements between the United States and other countries;
- to promote strategies to build global capacity for research on oral health; and
- to support collaborative research programs and protocols in line with NIDR's mission.

OIH also plans and implements international science exchange programs, sponsors and participates in international meetings and workshops, and disseminates research findings throughout the world. Joining the Associate Director in all these activities are the Special Expert for International Health and a new, full-time International Health Officer.

In recent years, NIDR has led an international effort to define an agenda for collaborative research on oral health. During FY 98, OIH adopted this agenda, to refine, refocus, and begin its implementation. The main topics of NIDR's international collaborative research agenda parallel the Institute's scientific programs. The topics include infectious and emerging infectious diseases, such as orofacial gangrene (noma); craniofacial anomalies, with particular emphasis on cleft lip and palate; optimum levels of fluoride for human organisms; oral cancer; biomaterials and biomimetics; human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS); and reduction of disparities in health through health promotion efforts. To promote research in these areas, OIH staff have begun to facilitate partnerships with other research sponsors and to provide "seed moneys" for researchers to plan and develop international research networks.

Previously, NIDR has been successful in funding individual awards that have led to multiple collaborative relationships and follow-up research activities between U.S. and foreign scientists in various regions of the world. While continuing this type of support, the Institute intends also to broaden and enlarge these effects by pooling resources globally for selected, well-defined, innovative projects. The aim is to strengthen promising lines of research that will deliver practical findings for improving health in communities worldwide.

In FY 98, OIH took a major step in this direction by developing a Request for Applications (RFA) for grants to plan international collaborative research on oral health. These grants will enable large-scale multinational and multidisciplinary teams to address scientific questions that require international collaboration. NIDR plans to award the grants during FY 2000 and hopes that they will stimulate researchers to submit follow-up applications for full-scale studies to be supported by U.S. or foreign funding sources or both. Information about these grants and other OIH activities can be accessed through the NIDR home page (http://www.nidr.nih.gov).

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Intramural Research

Osteoporosis Mouse Model

During FY 98, an international research team of NIDR scientists in the Craniofacial and Skeletal Diseases Branch created a new animal model for studying the development of osteoporosis. The team, which included scientists from China and Italy, developed the model by disrupting the gene for biglycan, a protein that is essential for tooth and bone formation. Targeted disruption of this gene in mice resulted in offspring with normal phenotypes, as evidenced by appearance and state of health. However, as the animals aged, their skeletal structure became markedly altered. The long bones showed pronounced malformations and loss of bone density. With this model, scientists have an unprecedented opportunity for studying osteoporosis and other genetic alterations associated with bone malformation. A report of this work was published in *Nature Genetics*.

Physiological Target for Anthrax Toxin

During FY 98, an international group of scientists identified a physiological target for the lethal action of anthrax toxin. The scientists included researchers from China, Iran, and Korea, in NIDR's Oral Infection and Immunity Branch. Anthrax toxin, a biological warfare agent, is composed of three polypeptides. When injected simultaneously, two of these proteins (protective antigen and lethal factor) cause death in rodents within 1 hour. Also, exposure to components of the toxin causes disruption of macrophages in mice within 2 hours. It was already known that protective antigen is a channel-producing protein and that lethal factor is a metalloproteinase, but the physiological target for lethal factor had not been identified. The NIDR researchers helped to show that mitogen-activated protein kinase-kinase (MAPKK) is the target for the proteinase. Lethal factor causes cleavage in MAPKK, disrupting the pathway for signal transduction among cells and thereby affecting their maturation and growth. If the specific site of cleavage can be identified, agents could be developed to block the action of lethal factor. A report of this work was published in *Science*.

Tumor-Suppressor Protein

During FY 98, scientists in NIDR's Craniofacial Developmental Biology and Regeneration Branch enhanced understanding of how cancer cells proliferate, particularly oral cancer cells. Development of cancer is held in check by certain crucial genes, such as the recently discovered PTEN/MMACI tumor-suppressor gene. This gene encodes a phosphatase (PTEN) that resembles tensin, a cytoskeletal protein. Mutated, inactive forms of PTEN have been found in many and various human tumors. Scientists from China and Japan collaborated in research showing that PTEN interacts with focal adhesion kinase (FAK), an essential component in the signaling system of cells. This interaction results in a decrease of phosphorylated FAK in tumor cells and inhibition of focal adhesions and of migration and spreading of neoplastic cells. Conversely, loss of PTEN may lead to progression of cancer. In fact, further study showed that reexpression of the PTEN gene in certain cancer cells in culture restored more normal cellular behavior. The investigators are continuing their studies to define the conditions under which PTEN retards the invasion of tumor cells into the matrix of basement membranes. A report of this work was published in *Science*.

Extramural Research

Consortium for Craniofacial Defects

Throughout the world, every 3.3 minutes, a baby is born with a disfigured, malfunctional face, oral cavity, or both. The number of persons afflicted with these birth defects is extremely large, as are the numbers of defects and their causes. Researchers are just beginning to unravel the complex of genetic, environmental, and behavioral factors that act alone or in combination to disrupt normal craniofacial development. A major obstacle in this research is the difficulty of identifying sufficient numbers of patients and appropriate control subjects for epidemiologic and genetic studies. In FY 98, to help resolve this problem, NIDR accelerated its efforts to support and stimulate partnerships for international collaborative research in this area.

In June 1998, the National Advisory Dental Research Council (NADRC) approved the NIDR staff's concept for a multinational Consortium for Craniofacial Birth Defects. The aim of the consortium will be to stimulate the design of shared protocols and research on craniofacial anomalies. Staff developed the concept in response to recommendations from two advisory workshops for NIDR to increase support of international collaborative research on craniofacial anomalies. No mechanism exists to encourage and support U.S. participation in this research. NIDR anticipates that other NIH components, private foundations, the European Community, and other foreign sources will participate in funding the consortium. A contract will be awarded to support creation and administration of the group.

Also in June, NADRC approved another concept developed by NIDR staff—to support a prospective, international, multicenter clinical trial of folate intervention to prevent cleft lip with or without cleft palate. Research suggests that folate deficiency may be significantly involved in the etiology of these conditions. In addition, during FY 98, NIDR supported the efforts of the International Consortium for Oral Clefts Genetics. Staff participated in a meeting of the consortium in Baltimore, Maryland, in April 1998, where significant progress was made toward preparation of common research protocols for international epidemiologic and genetic studies.

These accomplishments and activities reflect the Institute's new emphasis on understanding the development of craniofacial tissues and preventing and treating craniofacial anomalies. This emphasis is consonant with the major recent advances in craniofacial research, as highlighted in the NIDR chapter of the *National Institutes of Health Annual Report of International Activities* for FY 97. Genetics is, and will continue to be, a major part of this research, because of the interaction of genetic determinants with environmental and behavioral determinants of health outcomes.

Noma

In FY 98, NIDR initiated support for an epidemiologic study of noma, a highly destructive orofacial gangrene that mainly affects malnourished children in impoverished countries. A supplemental award was made to an investigator at the University of Maryland, Baltimore. The parent grant, which NIDR also cofunds, was awarded under the International Training and Research in Emerging Infectious Diseases (ITREID) Program of the Fogarty International Center (FIC). The aim of the noma study, which is being conducted in collaboration with international organizations such as WHO, is to establish a research base for designing interventions against noma and the suspected precursor lesion, acute necrotizing gingivitis. Investigators are focusing on the environment, lifestyles, sanitation, food and water quality, and proximity to livestock and other animals in the communities being studied. Microbiological, immunologic, and histological samples are being collected for analysis.

In several sub-Saharan countries in Africa (e.g., Nigeria), the frequency of noma is estimated to be 1–7 cases per 1,000 population and as high as 12 cases per 1,000 in the most affected communities. The mortality rate for untreated cases is estimated at 70%–90%, and survivors of the disease usually have extensive orofacial mutilations and functional impairments. Prevention of noma is imperative, because of these effects and because reconstructive surgery is prohibitively expensive.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

In FY 98, OIH staff continued NIDR's involvement in the U.S.-Russian Micronutrient Malnutrition initiative of the Gore-Primakov Health Agreement. In collaboration with FIC, NIDR staff helped to plan an NIH orientation visit in March 1998 for the Russian team that is cooperating in this initiative. The Associate Director for International Health, NIDR, continued to serve as the U.S. lead for the Fluoride Group within the initiative and was given the Centers for Disease Control and Prevention (CDC) Group Award for her leadership. Future plans call for U.S. participation (a) in the development of a demonstration project for community water fluoridation in Russia and (b) in a site-assessment visit. NIDR is collaborating in this effort with the U.S. Agency for International Development, CDC, WHO, the Russian Ministry of Health, and the Russian Dental Association, as well as the multinational corporate sector.

Activities With International and Multinational Organizations

World Health Organization

The Associate Director for International Health serves as coordinator for the WHO Collaborating Center for Epidemiology, Prevention, and Treatment of Oral Diseases and Conditions. During FY 98, she stimulated and participated in the first meeting of all WHO Collaborating Centers for Oral Health, which was held in Nice, France, in June 1998, in conjunction with the annual meeting of IADR. OIH staff attending that meeting promoted continued networking among these centers and with other WHO collaborating centers in health throughout the Americas. WHO invited the NIDR center to collaborate in planning a 1999 meeting in Africa for donors involved in oral health. WHO also asked OIH staff to comment on a draft WHO document on environmental health criteria for fluoride use and fluorosis.

The Associate Director for International Health and the Special Expert for International Health, NIDR, met in June 1998 with the WHO transition team for reorganization under the new WHO leadership. WHO's Oral Health staff are part of WHO's Division of Noncommunicable Diseases. In December 1997, WHO staff from this division presented a seminar at NIDR on the collaboration between NIDR and WHO on the campaign against noma. Discussions with WHO continue and are focused on strengthening the collaboration between WHO and NIDR, which began in 1956. This partnership is critical to the implementation of international collaborative research projects on oral health.

The Associate Director continued to serve on the Technical Advisory Group for the Regional Oral Health Advisor, Pan American Health Organization (PAHO). She also represented NIDR, as well as the Fédération Dentaire Internationale (FDI) and the American Dental Association, at meetings of the Directing Council of PAHO.

European Union

Through the European Union-U.S. Science Technology Agreement, OIH staff collaborated with FIC to foster relations with the European Union as a potential partner in international research on oral health. In May 1998, OIH staff visited the Office of the Science Counselor of the European Union, in Washington, D.C., to discuss collaboration in three areas of special interest: craniofacial anomalies, fluorides, and noma. Also, an NIDR researcher participated in a training program in Brussels, Belgium, for U.S. Government officials collaborating with the European Union.

Fédération Dentaire Internationale

The NIDR Director and staff prepared a number of scientific presentations for FDI's 1998 World Dental Congress, in Barcelona, Spain, in October 1998. The Associate Director for International Health, NIDR, helped to plan this meeting and participated in an FDI special consultation meeting on strategic planning for global promotion of oral health. She continued to serve as a consultant to FDI's Congress and Education Committee and contributed substantially to the planning of future World Dental Congresses, which will be held in Mexico City, Mexico, in 1999; in Paris, France, in 2000; and in Kuala Lumpur, Malaysia, in 2001. The Associate Director also served as the representative of IADR's Behavioral Scientists and Health Services Research Group to the FDI General Assembly.

International Association for Dental Research

The annual meeting of IADR was held in Nice, France, in June 1998. NIDR staff presented research findings during several sessions and symposia; met with representatives of international organizations to discuss opportunities for collaborative research and research training; staffed an NIDR information booth; and conveyed NIDR opportunities to individual researchers. In celebration of NIDR's 50th anniversary, Institute staff showed a 50th anniversary videotape and the Director, NIDR, presented remarks.

During the meeting, the Associate Director for International Health, NIDR, chaired a symposium on the WHO International Collaborative Study of Oral Health Outcomes, at which OIH staff described the impact of the study in the United States. Pertinent to NIDR's international collaborative research agenda, the Associate Director and other NIDR staff participated in the highly successful Oral-Facial Gangrene (Noma) Symposium and in a meeting on fluoride activities. The proceedings of the symposium on noma, which was a joint WHO-NIDR initiative, will be published in the *Journal of Oral Diseases* in 1999. In 1994, WHO launched an International Action Network Against Noma, and NIDR's WHO collaborating center is part of this network.

American Dental Association

The Associate Director for International Health continued to serve as consultant to the Council on American Dental Association Sessions and International Relations.

Fogarty International Center

The Associate Director for International Health continued to represent NIDR at the NIH international representative meetings coordinated by FIC. She also served on a committee to develop a draft document on Models for Collaborative Funding With Foreign Entities. OIH responded to requests from FIC and the NIH for suggestions and comments on WHO's reorganization and other international health items.

Other Activities

In FY 98, the Associate Director for International Health, NIDR, served on the international advisory committee for the D. Walter Cohen Middle East Center for Dental Education, Jerusalem, Israel. This institution, named after an NADRC member, provides a bridge for peace and cooperation in the fields of dental education and research for all peoples in the region. The advisory committee met for the first time, in Israel, in November 1997, to identify funds for fellowships and other educational initiatives and to discuss possible research initiatives of common interest. While in Israel, the Associate Director met with the chief scientist of the Ministry of Health, to discuss opportunities for collaborative research. She also led a seminar on opportunities for international research collaboration, for faculty members of the Hebrew University-Hadassah School of Dental Medicine, Jerusalem, and met with faculty at the university's School of Public Health and Community Medicine.

In December 1997, an NIDR oral surgeon in the Division of Intramural Research led an Operation Smile mission to Hanoi, Vietnam. The delegation, which consisted of dental students and faculty from the University of Maryland, Baltimore, provided oral surgery and routine dental care to patients in need of these services.

During the annual meeting of the American Association for Dental Research, in Minneapolis, Minnesota, in March 1998, OIH staff met with researchers and industry representatives to discuss the fluoride initiative of NIDR's international collaborative research agenda. A document describing this initiative was amended and completed, and the 10 hypotheses developed will be reviewed by a larger working group in 1999. Other NIDR activities related to fluoride use included the participation of NIDR staff (a) in the Workshop on Salt Fluoridation, in Quito, Ecuador, and (b) in discussions at the Japan Association for the Promotion of Fluorides for Preventing Tooth Decay, in Nagasaki.

NIDR and the NIH Office of Research on Women's Health contributed support for the first International Leadership Conference on Global Alliances Advancing Education, Research, and Women's Health. This landmark conference, which was held in Cannes-Mandelieu, France, in June 1998, was a collaborative effort led by the American Association of Dental Schools in partnership with other major dental organizations and supported by additional funding from private industry and foundations. Representatives from 18 countries on six continents attended, and 30 speakers addressed global aspects of leadership for women in education, research, and women's health. The Associate Director for International Health and other NIDR staff gave presentations on women's health research supported by NIDR and on mechanisms for international collaborative research relevant to women's health. The proceedings will be published in the *Journal of Dental Education* in March 1999, and a follow-up conference is being planned for Washington, D.C., in 2000.

NIDR staff attended the 12th World AIDS Conference in Geneva, Switzerland, in late June and early July 1998. NIDR staff and grantees gave presentations on the oral manifestations of AIDS, focusing particularly on women and including research findings from the NIH-supported Women's Initiative Health Study. While attending the annual IADR meeting in Nice, France, in June 1998, staff met with organizers of the 4th International Workshop on the Oral Manifestations of HIV Infection, to complete plans for that workshop, which will be held in South Africa, in 2000, in conjunction with the 13th World AIDS Conference.

For the annual meeting of the International Sociological Association, in Montreal, Quebec, in July 1998, the Associate Director for International Health, NIDR, coauthored a presentation on changing currents in dentistry and dental education.

In addition, during FY 98, the Director, NIDR, participated in an NIH briefing for the Minister of Health of Canada and his delegation. The Associate Director for International Health and other NIDR staff concluded a 1-year training program to inform a South Korean science administrator about the NIH and its grants administration. NIDR also hosted a Japanese scientist from Tokyo Medical and Dental University, who presented a lecture on the status of oral health in Japan to NIDR staff.

An NIDR investigator continued to strengthen skills in health promotion research through a study program at the University College London Medical School, England, and participated in a number of international meetings on health promotion, including the 1st United Kingdom Conference on Health Promotion Research. This investigator also is collaborating on a research grant supported by the United Kingdom Department of Health, to develop and test outcome measures for health promotion research in primary care settings.

Also, OIH staff and other NIDR staff responded to inquiries about opportunities for collaborative research at NIDR and the NIH, from scientists in Bulgaria, China, the Czech Republic, Malaysia, Norway, Russia, South Africa, Thailand, and the United Kingdom.

Extramural Programs

In FY 98, extramural activities included 6 foreign grants, 18 domestic grants with foreign components, and 1 domestic contract with a foreign component. Of these, one foreign grant, four domestic grants with a foreign component, and the contract were new awards in FY 98. This extramural international activity directly involved research institutions and scientists in 21 countries and Taiwan. The countries were Belgium, Brazil, Canada, China, Denmark, Egypt, India, Israel, Japan, Jordan, Mexico, Nigeria, Norway, the Philippines, Portugal, Senegal, Sudan, Sweden, Turkey, the United Kingdom, and Vietnam. The research conducted was integral to the six scientific programs in NIDR's Division of Extramural Research, as described here.

Inherited Diseases and Disorders Program

NIDR's Inherited Diseases and Disorders Program included support for two foreign grants and eight domestic grants with a foreign component. Among the six scientific programs, this international activity was the largest in number of awards and dollars, reflecting the Institute's expanded focus on craniofacial diseases and disorders. One-fourth of all birth defects include craniofacial malformations, and frequently, the persons affected require multiple surgeries and other substantial treatments, beginning in early infancy. NIDR's objective in this program area is to promote research that advances understanding of the underlying causes of these defects and, thereby, to enhance prevention, diagnosis, and treatment.

Cleft Lip and Cleft Palate

In three new studies, investigators are analyzing the contribution(s) of genetic or environmental factors, or both, to cleft lip with or without cleft palate. With NIDR support, an investigator at the University of Aarhus, Denmark, is using Danish cases of these conditions and control groups for these analyses. Another investigator, at the University of Pittsburgh, Pennsylvania, is collaborating with investigators at the University of Calgary, Alberta, and Hacettepe University, Ankara, Turkey, to study an inbred Turkish population with inherited nonsyndromic cleft lip with or without cleft palate. In related work, this investigator continued a long-term study to identify genetic loci for these conditions in Asian populations and in European white populations. This research effort was expanded in Shanghai, China, and was enlarged to allow comparison with a white population in West Bengal, India.

A third new study funded by NIDR in FY 98 is being conducted by an investigator at Ohio State University, Columbus. In collaboration with a researcher at the Jordan University of Science and Technology, Irbid, this investigator is focusing on families in Jordan, where cultural practices of consanguineous marriages and high birth rates, combined with an expected high incidence of cleft lip with or without cleft palate, will be advantageous for identifying genetic loci for these conditions.

In some single-gene craniofacial disorders, clefting malformations are associated with mutations of the gene for transforming growth factor α (TGF-α). Recently, a researcher at the University of Iowa, Iowa City, also documented associations between these malformations and TGF-β3, as well as interactive effects between TGF-α and smoking. These findings resulted from NIDR-supported research conducted initially in the Philippines and then extended to Denmark, Japan, and Vietnam. The three newly funded studies will complement this work and will be useful for determining whether the same gene–environment associations occur in more homogeneous populations. Other genes linked to clefting malformations also may be identified.

While these and other researchers aim to clarify the genetic and environmental aspects of cleft lip with or without cleft palate, other investigators are focusing on improving surgical treatment for these malformations. Cleft lip and palate is one of the most common congenital malformations, occurring in about 1 in 750 births. Surgical repair, which typically is performed within a child's 1st 2 years, generally is associated with retrusion of the upper jaw. Due to evidence suggesting that this aberration is related to surgical repair of the lip, NIDR has been supporting a prospective randomized controlled study to assess outcomes of two surgical techniques for repairing cleft lip. This study, which ended its 2nd year in FY 98, involves collaboration between investigators at the University of Florida, Gainesville, who are using one technique, and investigators at the University of São Paulo, Brazil, who are using another method. The study will include 200 infants with cleft lip and 200 infants without cleft lip.

As part of this study, other investigators at the same institutions are comparing the effects on the level of speech competence of two surgical approaches for repairing cleft lip and palate. Recruitment of about 600 children for this prospective randomized clinical trial continued in FY 98. Final outcomes are expected in 1999.

A related study is nearing completion. Investigators have conducted a 5-year, prospective, multicenter clinical trial to determine the relative effectiveness of two surgical procedures for correcting insufficiency of the soft palate and pharynx after repair of cleft palate. The participating institutions are Children's Hospital, Los Angeles, California; Loma Linda University Medical Center, California; the University of North Carolina, Chapel Hill; and the University of Oslo, Norway. The final data analyses and report are expected soon.

Formation of Teeth and Bones

A scientist at the Weizmann Institute of Science, Rehovot, Israel, continued to define the structure of proteins involved in the formation of teeth and bones. Information gained from these studies will enhance understanding of how teeth and bones are formed and how they function mechanically. For example, although it is known that ongoing crystal growth in bone adversely affects the bone's fracture properties, the structural basis for this phenomenon is not well understood. In clarifying this structure and the relationship between structure and function in bone or teeth, the investigator is obtaining information that has immediate implications for treating diseases (e.g., osteoporosis) that affect these tissues.

Nutrition and Development

An investigator at Hampshire College, Amherst, Massachusetts, continued to follow up a cohort of children in Egypt and Mexico, to define the relationship between dietary intake of nutrients and development of tooth enamel. This study, which is nearing completion, offers a unique opportunity for understanding the relationship between nutrition and development through a longitudinal and prospective approach.

Infectious Diseases Program

NIDR's Infectious Diseases Program included support for one foreign grant and two domestic grants with foreign components. In collaboration with FIC, NIDR also cofunded 13 ITREID awards; provided a supplemental grant for 1 ITREID award; and cofunded 3 awards under FIC's AIDS International Training and Research Program (AITRP). The Infectious Diseases Program supported the second largest amount of international activity in the extramural program, reflecting the importance of emerging and reemerging infections worldwide. The complex environment of the oral cavity presents a formidable challenge for selectively controlling pathogenic microbes that infect and reinfect hard and soft oral tissues of both healthy persons and those with compromised immunity.

Herpesvirus

An investigator at Eastman Dental Institute and Hospital, University of London, England, continued to explore the oral implications of human herpesvirus 8 (HHV-8). This researcher is applying a highly sensitive and technically difficult technique to identify cell types in the oral mucosa that support HHV-8 infection; to clarify the association of

HHV-8 with Kaposi's sarcoma and HIV; and to evaluate the role of saliva in transmission of HHV-8. The investigator has substantial archival samples of oral tissue and has prospects for obtaining samples from other countries.

HIV Infection

NIDR also continued support for a clinical epidemiology study of oral lesions in heterosexual women and men in Senegal who may or may not be infected with human immunodeficiency virus type 1 (HIV-1), human immunodeficiency virus type 2 (HIV-2), or both. The study is being conducted by an investigator at the University of Washington, Seattle, in collaboration with the University of Dakar, Senegal. Oral lesions are found in a substantial number of HIV-infected persons, and the incidence of HIV infection is greater in developing countries such as Senegal. However, few systematic studies of the epidemiology of HIV-associated oral disease in the populations of these countries have been undertaken, and no published data on the risk of oral pathology associated with HIV-2 are available. The investigator is using and building on a clinical infrastructure already developed for cross-sectional and cohort studies of HIV and neoplasia.

Oral Bacteria

Investigators at the University of Oklahoma Health Sciences Center, Oklahoma City, and the University of Newcastle upon Tyne, England, continued to collaborate on a study of the genetics of sugar metabolism in *Streptococcus mutans,* bacteria that metabolize sugar and foster dental caries. Their studies are focused on clarifying the genetic variability of the bacteria, cloning and inactivating genes to study metabolic mechanisms of control, and analyzing the structure and function of the bacteria. This research is providing essential background information on the genes of *S. mutans* that are involved in the survival of these bacteria and in the formation of sugar polymers that protect them and foster their adherence to teeth.

Emerging Infectious Diseases

For a 2nd year in FY 98, NIDR cofunded research and training for participants from developing countries in 13 ITREID centers at universities in the United States. These centers provide a focus for strengthening the research infrastructure and personnel to address emerging and reemerging infectious diseases worldwide. In collaboration with FIC, NIDR also supported a supplemental award for an ITREID grant to study the devastating disease, noma. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

AIDS

In addition, NIDR initiated cofunding of three AITRP awards. The 5-year awards were made to investigators at the University of California School of Public Health, Berkeley; the University of Maryland, Baltimore; and the University of Washington, Seattle. NIDR funds are being used to train oral health professionals from developing countries to address the AIDS epidemic more effectively through research. Oral health professionals will be recruited for training, from the following countries: Barbados, Botswana, Brazil, Côte d'Ivoire, Jamaica, Kenya, Mozambique, Peru, Thailand, Trinidad and Tobago, Vietnam, and Zimbabwe.

Neoplastic Diseases Program

International activities in NIDR's Neoplastic Diseases Program included support for three domestic grants with foreign components, two of which were new awards. The researchers are addressing the causes and treatment of neoplastic diseases, which are two of the four main areas in this Program. The four program areas are causes and early detection of oral cancers; occurrence, progression, and recurrence of second primary lesions; invasion and metastasis by oral cancer cells; and therapies for oral cancers and secondary conditions.

Vaccines for Oral Cancer

For a 2nd year in FY 98, investigators at the University of Pittsburgh, Pennsylvania, and the Ludwig Institute for Cancer Research, Brussels, Belgium, collaborated on the development of vaccines for oral cancer. The investigators are identifying and characterizing new immunogenic peptides derived from squamous cell carcinomas and are making synthetic peptides from the mutated p53 tumor-suppressor gene, for use in stimulating lymphocytes to kill oral tumor cells. They are also exploring the role of interleukin 12 in enhancement of immune responses to combat oral tumor cells. The Belgian collaborator has used oral cancer cells to clone tumor-specific peptides, which will be used in research on enhancing the immune response against oral tumors.

Genes for Gingival Fibromatosis

In a new study, an investigator from Bowman Gray School of Medicine, Winston-Salem, North Carolina, is collaborating with other investigators to identify and characterize genes that cause hereditary gingival fibromatosis—a condition involving overgrowth of the keratinized tissues surrounding the teeth. The other participants in this study are from the Center for Human Genetics, Louvain, Belgium, the State University of Campinas, Piracicaba, and the University of Taubaté, São Paolo, Brazil. Tissue samples will be obtained from Brazilian families affected by this disease, and the Belgian investigator, who is an expert on the disease, will provide consultation on the delineation of genetic aberrations. The investigators will use molecular and cytogenetic approaches to map the loci of candidate genes and to identify specific gene mutations.

Markers of Risk for Oral Cancer

NIDR made another new award, to an investigator from Temple University, Philadelphia, Pennsylvania, for a proposed collaboration with a researcher from Khartoum, Sudan, to identify persons who may be genetically susceptible to oral cancer, because of abnormalities in genes that encode enzymes involved in the metabolism of tobacco carcinogens and alcohol. The investigators plan to compare the polymorphisms in these genes with mutations in the p54 gene, a known tumor suppressor, and plan to examine race as a possible factor in susceptibility to oral cancer that is associated with specific genotypes for carcinogen-metabolizing enzymes. Populations in Sudan have an unusually high frequency of oral cancer.

Chronic Disabling Diseases Program

NIDR's international activities in the Chronic Disabling Diseases Program included three foreign grants and one domestic grant with a foreign component. These grants focus on two major chronic conditions affecting the dental, oral, and craniofacial complex: dental and orofacial pain and temporomandibular joint (TMJ) disorders. Other conditions addressed by the Program include osteoporosis and related bone disorders; neuropathies and neurodegenerative diseases; autoimmune diseases (e.g., Sjögren's syndrome); and oral conditions (e.g., periodontitis) related to systemic diseases (e.g., diabetes and cardiovascular disease).

Pain Mechanisms

Three investigators at the University of Toronto, Ontario, continued to clarify the brain stem mechanisms involved in dental and orofacial pain. One investigator showed that C fibers (small nerves) in dental pulp induce changes in the central nervous system that enhance the reception of painful stimuli to teeth. The mechanism for this effect appears to involve the neurotransmitter NMDA. Synthetic compounds that block the action of NMDA (NMDA antagonists) have been discovered recently. The researcher's findings suggest that these antagonists may be useful for alleviating dental pain associated with inflammation.

The second investigator reported additional findings that support the importance of central nervous system NMDA in pain reception. This investigator found that activation of C fibers in the TMJ produces enhanced pain reception in the central nervous system through an NMDA-dependent mechanism. Further research showed that a second mechanism in the central nervous system is triggered by activation of C fibers. This opioid mechanism, which produces a morphine-like effect, limits sensitization to pain. The third investigator completed studies of neurons in the thalamus that respond to thermal stimulation of the central nervous system. The research of these investigators is complementary and provides evidence of pain mechanisms in the central nervous system that may be amenable to pharmacological control.

Temporomandibular Joint Function

Investigators at the University of Washington, Seattle, and the University of British Columbia, Vancouver, continued to collaborate on the development of experimental models for studying the function and mechanics of the TMJ. The goal of this work is to understand the biochemical environment of the TMJ and to elucidate the effects of alterations in this environment on remodeling or degeneration of the joint. Experimental data have confirmed that the TMJ of pigs is a relevant model for humans. During FY 98, the investigators determined that a pig's TMJ is loaded compressively and substantially during jaw closure. These findings may explain why certain materials used to replace the TMJ disc in humans fail. The investigators also validated a computer model of TMJ function in the pig, which suggests that computer modeling of jaw function in humans is possible.

Biomimetics, Tissue Engineering, and Biomaterials Program

NIDR's Biomimetics, Tissue Engineering, and Biomaterials Program included one domestic contract and two domestic grants with foreign components. The aim of the Program is to encourage research on the development of natural and synthetic materials used to repair, regenerate, restore, and reconstruct oral and craniofacial tissues and organs. Ensuring biocompatibility and satisfactory performance are two major issues for the three components of this Program. Assessing the oral and systemic effects of dental amalgam is a related issue.

Performance of Composites

Investigators at the University of Florida, Gainesville, and the University of Louvain, Belgium, continued to collaborate on clinical evaluations of composite materials used to restore posterior teeth. They are focusing especially on the performance (i.e., wear resistance) of these materials.

Effects of Dental Amalgam on Health

Investigators at the University of Washington, Seattle, and the University of Lisbon, Portugal, are collaborating in the Casa Pia Study of Dental Amalgams in Children. This clinical trial involves 500 children, ages 8–10 years, who are students at the Casa Pia Schools in Lisbon and who need extensive dental restorative treatment. All the children receive dental care and are randomly assigned to one of two treatment groups. Tooth restoration is performed with dental amalgam in one group and with composites in the other group. The objective is to determine whether dental amalgam affects health in children, a population that may be most susceptible to such effects. During FY 98, the investigators completed recruitment for the study and conducted follow-up visits with children who were enrolled in FY 97.

Amalgam and Resistant Bacteria

Under a new contract, another investigator at the University of Washington, Seattle, is assessing the effect of dental amalgam on the development of resistance by oral bacteria to antibiotics or mercury. Specific aims include determining whether treatment with dental amalgam or composites alters the prevalence of oral bacteria that are resistant to antibiotics or mercury and whether acquisition of resistant bacteria in the oral cavity is linked with enteric acquisition of such bacteria. The investigator is obtaining and assaying oral and urine samples from 150 of the children participating in the Casa Pia Study.

Behavior, Health Promotion, and Environment Program

NIDR's Behavior, Health Promotion, and Environment Program included two domestic grants with a foreign component. International studies can be particularly informative for this Program, which addresses the interactive role of socioenvironmental, behavioral, genetic, and biomedical factors in dental, oral, and craniofacial diseases and conditions.

Oral Health of Older Adults

Investigators at the University of Washington, Seattle, and the University of British Columbia, Vancouver, are in the 2nd year of a 5-year clinical trial to test whether rinsing with chlorhexidine and fluoride reduces tooth loss in an ethnically diverse population of adults aged 60–75 years who previously had oral disease and irregular dental care. Participants are recruited at both sites and are given baseline dental examinations. Those who are enrolled in the trial have at least four teeth and have not visited a dentist in the past 2 years. The Canadian group includes persons recruited through senior centers, especially centers serving the Indo-Chinese population of Vancouver.

Cultural Aspects of Pain

Another investigator at the University of Washington, Seattle, continued to collaborate with researchers in Denmark, Sweden, and Taiwan in a 5-year study to evaluate how patients and health care providers view acute and chronic pain. Researchers have obtained and compared qualitative data on pain associated with labor and childbirth, tooth drilling, and persistent facial or jaw pain. In some of the data reported in FY 98, Anglo-American dentists described their patients, particularly younger patients, as feeling they had a "right" not to feel any pain, especially when local anesthesia is used. In contrast, dentists in China and Scandinavia did not perceive that their older or younger patients expected total relief from pain during tooth drilling. Similarly, Anglo-American dentists described local anesthesia as typically necessary for tooth drilling, whereas dentists from China and Scandinavia thought that encouraging deep breathing or giving a reassuring touch were generally sufficient to help patients cope with transitory discomfort.

In a related qualitative study, the same investigators assessed patients' strategies for coping with acute pain. Although Anglo-American patients typically expected drugs or injections to be used to prevent acute pain, they also reported using distraction strategies, which were rarely noted by Chinese patients. Chinese patients emphasized use of externally applied salves, oils, or creams to reduce pain. Additional cross-cultural studies are needed to further define the expectations of patients and health care providers regarding pain and coping strategies in different health care systems. Enhanced understanding of the effect of cultural influences on perceptions of pain and on strategies for coping with pain will be useful for improving communications between patients and providers about diagnosis and treatment of pain.

International Meetings

In FY 98, NIDR supported 16 international conferences, most of which were held in the United States. The four Gordon Research Conferences addressed the following topics: cellular and molecular mycology; proteoglycans; biomineralization; and fibronectin, integrins, and related molecules. Other conferences included the International Symposium on Olfaction and Taste; the 5th International Symposium on Streptococcal Genetics; the Annual Symposium on Ceramics in Medicine; and the 5th Research Workshop on Head and Neck Cancer.

Five conferences were held in other countries: Bioartificial Organs: Science, Medicine, and Technology, in Alberta, Canada; the China-U.S. Workshop on the Role of Saliva in Oral Health, in Beijing, China; the 1st International Leadership Conference on Global Alliances Advancing Education, Research, and Women's Health, in Cannes-Mandelieu, France; the 6th International Conference on Chemistry and Biology of Mineralized Tissues, in Vittel, France; and the 6th International Conference on Oral Cancer, in New Delhi, India.

In addition, more than 60 NIDR scientists and science administrators participated in international conferences, seminars, or meetings held in the United States and abroad. They traveled to 24 countries and Taiwan to give lectures or keynote speeches; chair scientific sessions; attend planning meetings; present courses and seminars; discuss collaborative studies; and exchange information on research advances and opportunities in dental, oral, and craniofacial health. In association with international meetings, staff presented talks at local universities, visited scientific laboratories to discuss or conduct collaborative research, and provided consultation on matters of oral health.

Both the NIDR Director and the NIDR Scientific Director extended their leadership to this international outreach. The NIDR Director was invited to speak on Clinical Dentistry in the 21st Century, to open the 1st International Continuing Education Programme, at the Pierre Fauchard Academy, in London, England. He presented an address in Manchester, England, to celebrate the 50th anniversary of the Royal College of Surgeons of England and the 50th birthday of the British Dental Association. At IADR's annual meeting, in Nice, France, the Director chaired a session on Craniofacial Development and Anomalies and Their Therapies. In addition, he made a presentation entitled The Oral Cavity and Gene Therapy, at the 30th anniversary conference of the European Research Group for Oral Biology, which focused on Oral Biology at the Turn of the Century: Misconceptions, Truths, Challenges, and Prospects. The conference was held in Interlaken, Switzerland. The Director also coauthored publications of his laboratory work in two international journals.

NIDR's Scientific Director met with scientists in Denmark, England, France, Japan, South Africa, and Switzerland. In Denmark, he discussed ongoing research collaborations with investigators at the University of Copenhagen, and later in FY 98, he chaired a session at the meeting on Proteases and Protease Inhibitors in Cancer, in Nyborg. In Manchester, England, he participated in the organization of the 1998 annual meeting of the European Research Group for Oral Biology. In France, he participated in IADR's annual meeting, in Nice.

Traveling to Japan on two occasions, the Scientific Director gave presentations at the University of Okayama Dental School and the University of Osaka; visited oral health investigators in industry in Toyama; and presented a seminar at the 40th annual meeting of the Japanese Association of Oral Biology, in Nagoya. At the University of Witwatersrand, Wits, South Africa, he gave a lecture, entitled Frontiers of Science in Dentistry, and discussed research and possible collaborations. The Scientific Director also participated in meetings of the International Association of Dentistry and the World Congress on Preventive Dentistry, in Cape Town, South Africa. At the world congress, he led a workshop on Science and Skills Transfer and delivered two lectures. In Interlaken, Switzerland, the Scientific Director participated in the 30th anniversary conference of the European Research Group for Oral Biology, at which he cochaired a session on Challenging the Paradigms.

Intramural Programs and Activities

The NIDR Division of Intramural Research continued its international leadership and outreach during FY 98. Scientists throughout the Division engaged in many activities. They collaborated with investigators at foreign laboratories; organized and chaired sessions at major international meetings; presented invited lectures and research findings; provided consultation on the direction and progress of research; supplied important biological reagents to other scientists and laboratories around the world; reviewed research grants for foreign institutions; served as external advisors for young investigators at foreign institutions; coauthored numerous publications with foreign scientists; and published reports of research in numerous international journals.

In addition, more than 120 foreign scientists collaborated with U.S. investigators in NIDR's intramural laboratories. These scientists represented 26 countries and Taiwan. The largest proportion of scientists (50%) came from two countries: China and Japan. About 20% came from three other countries: Israel, Korea, and the United Kingdom. Another 23% came from the following 11 countries: Argentina, Brazil, Canada, Denmark, France, Germany, India, Italy, the Netherlands, Russia, and Spain. Ten other countries and Taiwan also were represented. The 10 countries were Australia, Belgium, Bulgaria, Greece, Iran, Mexico, New Zealand, Norway, the Philippines, and Switzerland. NIDR intramural investigators also collaborated on research projects at institutions in 21 countries and Taiwan.

During FY 98, NIDR's Division of Intramural Research added two research units, the Molecular Structural Biology Unit and the Functional Genomics Unit, to complement its seven branches.

Craniofacial Developmental Biology and Regeneration Branch

Researchers in NIDR's Craniofacial Developmental Biology and Regeneration Branch are studying the cell biology and molecular biology of craniofacial development and regeneration, as well as developmental mechanisms. In the Developmental Mechanisms Section, Postdoctoral Fellows from Bulgaria, China, France, Israel, Japan, and the Netherlands contributed their expertise to investigations of the specific interactions of cells with extracellular matrix or other cells. They explored the effects of these interactions on signal transduction within cells, selective expression of genes, and organization of the cytoskeleton. The researchers continued to elucidate the regulation of these processes in adhesion, migration, growth, and differentiation of cells and studied other processes critical to embryonic development, tissue remodeling, and malignant disorders. Understanding of these processes could lead to new approaches for prevention and treatment of disease. The Chief of the Section is an elected council member of the International Society for Matrix Biology.

Scientists in the Cell Biology Section are studying the structure and function of the extracellular matrix by using model systems of endothelial cells for studies of angiogenesis, tumor cells for understanding metastasis, and salivary gland cells for studies of differentiation. During FY 98, scientists from Germany, Israel, and Korea contributed to studies of tumor metastasis; investigators from Israel and New Zealand worked on the differentiation of salivary gland cells; and a physician from Spain participated in the research on endothelial cells and angiogenesis. The Chief of the Section is an honor roll member of the International Union Against Cancer and an internationally elected member of the Metastasis Research Society Board.

In the Molecular Biology Section, scientists from Canada, Denmark, France, Germany, Japan, and Korea studied the structure and function of components of the basement membrane. They identified active sites of laminin chains and elucidated the roles of the components in development and disease. Researchers from Canada and Japan used animals models, which they had developed for understanding cartilage development and diseases, to study the genes that control transcription in cartilage. Scientists from Japan, Korea, and Spain conducted an oral genome project to identify important genes for the development of teeth and craniofacial tissues. Some of the work of the Japanese scientists was supported by funds from the Japanese government and from the Japan Society for the Promotion of Science Fellowship. The Chief of this Section is a member of the Japan Society of Extracellular Matrix Advisory Board.

Craniofacial and Skeletal Diseases Branch

Investigators in NIDR's Craniofacial and Skeletal Diseases Branch are studying the formation and repair of craniofacial and skeletal tissues (e.g., bone and cartilage). In the Developmental Biology, Skeletal Biology, and Skeletal Clinical Studies Program, NIDR scientists are focusing on the factors that regulate formation of skeletal elements during development and on the biochemistry of bone marrow stromal cells and their role in mediating skeletal metabolism in health and disease. These cells are unique in that they are able to form bone, cartilage, adipocytes, stroma that supports hematopoiesis, and perhaps even muscles, tendons, and ligaments. During FY 98, scientists from Italy and Russia helped to biochemically characterize bone marrow stromal cells and to determine how they differ from stromal cells of tissues that are unable to form bone. Other scientists, from Israel and Italy, collaborated in these studies and in determining the pathophysiology of fibrous dysplasia, a genetic but noninherited disease affecting bone. A scientist from the United Kingdom identified a factor that may regulate commitment of cells to form skeletal elements.

In collaboration with investigators in Italy, NIDR scientists determined that the G protein has a critical role in regulating osteogenic (bone-forming) activity. When this protein is mutated, as in fibrous dysplasia of bone, osteogenesis is blocked, leading to the replacement of normal bone and marrow with highly fibrotic, structurally unsound tissue. The investigators created a model system of this disease in mice to further study the formation of these lesions and to develop new therapies. In collaboration with investigators in Israel and Italy, NIDR scientists also designed and began implementation of the largest and most definitive clinical study of fibrous dysplasia of bone in the world. This study involves a number of international associate investigators and the European Pediatric Orthopaedic Society, which will gather from its members data on the surgical treatment of this disease.

In the Molecular Biology of Bones and Teeth Unit, NIDR scientists are working to produce animal models to study the function and regulation of the genes for mineralized tissues. The creation of a mouse model of osteoporosis was a major achievement in FY 98. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.") A scientist from the Netherlands completed analysis of an immortalized strain of stromal fibroblasts from human bone marrow that have a mutation in the estrogen receptor α. The scientist determined that, in the absence of this receptor, estrogen can continue to function through alternative, genetic regulatory mechanisms. In addition, an investigator from Switzerland participated in the development of mice that are genetically altered with a mutated gene for bone sialoprotein (BSP) and with promoter DNA that enhances transcription of the BSP gene. The investigator will be studying the cell biology of tissues involved in the expression and control of BSP.

In the Protein Chemistry Unit, NIDR scientists are studying the structure and function of extracellular proteins of bones and teeth and the function of G protein. During FY 98, scientists from Germany, Israel, and Italy collaborated on experimental studies of the G protein mutation that occurs in McCune-Albright syndrome, a fibrous dysplasia of bone. Scientists from Belgium and Italy investigated the possible function of proteins that are secreted in various cancers related to nutrition in bone.

The Chief of the Branch served on the editorial board of *Calcified Tissue International;* the international advisory board of the *Japanese Journal of Bone and Mineral Research;* and the program committee for the 2nd Joint Meeting of the American Society of Bone and Mineral Research and the International Bone and Mineral Society. The Branch Chief also was a reviewer of grants for organizations in Canada and Italy that fund research. The Chief of the Molecular Biology of Bones and Teeth Unit was a member of the editorial board of *Calcified Tissue International,* consulted on a binational grant with Israel, and was an external advisor for a Danish fellowship awardee and for a researcher at the University of Toronto.

Gene Therapy and Therapeutics Branch

Investigators in NIDR's Gene Targeting and Therapeutics Branch are applying genetic tools to elucidate the function and dysfunction of salivary glands. In the Gene Transfer Section, scientists are using different vectors to transfer genes into salivary gland cells, to address significant biological questions or explore therapeutic benefits. During FY 98, investigators from China, Israel, and the United Kingdom contributed to these studies. The Chief of the Section was associate editor for the *European Journal of Dental Education;* lectured at Tokyo Dental College, Japan; served as an external referee for promotion and tenure at universities in Australia, England, and Israel; and prepared an invited review for the *Journal of the Israeli Dental Association.*

Research in the Secretory Physiology Section is focused on mechanisms that regulate calcium and, particularly, calcium signaling in salivary gland cells. In collaboration with a scientist at Hebrew University, Jerusalem, Israel, NIDR scientists are studying the role of transition metal ions in radiation-induced damage to salivary glands. This work is funded by the U.S.-Israel Binational Foundation.

Investigators in the Membrane Biology Section are studying the structure, function, and regulation of membrane transport proteins involved in the secretion of exocrine fluid. Of special interest is the secretory Na^+ K^+ 2 Cl^- cotransporter, the ion transport system responsible for most of the fluid secretion by many salivary glands. A researcher from Japan participated in studies of the expression of this cotransporter in yeast. The aim is to obtain a sufficient amount of the protein to study its structure. Another Japanese scientist, on brief sabbatical leave, initiated studies to produce monoclonal antibodies against an important intracellular receptor.

In the Gene Regulation and Expression Unit, scientists are developing gene-transfer vectors that can be used for laboratory and clinical studies. During FY 98, a scientist from China worked on the development of novel hybrid vectors that could deliver infection or chromosomal integration efficiently. Scientists from Denmark and Japan contributed to studies of gene expression and the development of salivary glands. A scientist from Japan studied the bioactivity and spectrum of activity of adenoviral vectors encoding the antifungal protein, histatin.

Scientists in the Clinical Investigations Section are studying the mechanisms of autoimmune-mediated exocrinopathies and are conducting clinical trials of new therapies for salivary gland dysfunctions. A scientist from China studied the expression of cytokines in human salivary glands, and a scientist from Japan worked on the expression of cytokines in animal models of Sjögren's syndrome. An investigator from Israel examined Fas-mediated apoptosis (cell death) in salivary glands and methods for noninvasive diagnosis of the involvement of salivary glands in Sjögren's syndrome. As president of the International Society for Oral Oncology, the Chief of the Section established a collaborative relationship between the society and the Multinational Association for Supportive Care in Cancer.

Oral Health Promotion, Risk Factors, and Molecular Epidemiology Branch

Investigators in NIDR's Oral Health Promotion, Risk Factors, and Molecular Epidemiology Branch are conducting gene-mapping and classic epidemiologic studies of oral cancer, nasopharyngeal carcinoma, and other craniofacial disorders. They are also identifying the bacterial causes of early-onset periodontitis and are developing more powerful statistical strategies for delineating genetic aspects of complex diseases. During FY 98, investigators from China and Taiwan played major roles in collaborative studies with scientists in Taiwan to map genes associated with nasopharyngeal carcinoma and to understand the molecular genetic epidemiology of oral cancer. NIDR scientists also explored possible expansion of this research to mainland China. In addition, a Branch scientist collaborated in analyses of samples from case patients and control subjects in a study of oral cancer in Greece. The work included development and testing of improved methods for detecting human papillomavirus. In collaboration with a scientist in Poland, this scientist also conducted large-scale genome-scanning studies of DNA from patients with Kartagener's syndrome, an inherited disorder.

A scientist from Norway guided the Branch's work on early-onset periodontitis. Major advances accomplished during FY 98 include identification of several bacterial species that are associated more strongly with severe early-onset periodontitis than are other species; development of an improved system for clinical classification of the disease; and identification of β-glucuronidase in the gingival crevicular fluid of young persons, as a valuable marker of higher risk for the generalized form of early-onset periodontitis. The scientist from Norway coauthored two research reports for the annual meeting of IADR, in Nice, France.

Other scientists in the Branch coauthored two research reports for a Genetics Analysis Workshop and the International Genetics Epidemiology Society meeting, both held in Arcachon, France. These reports addressed (a) linkage analysis of genetic traits for alcoholism and (b) the increases in statistical power gained from cluster-based tests for linkage, respectively.

Oral Infection and Immunity Branch

Researchers in NIDR's Oral Infection and Immunity Branch are studying infectious and parasitic diseases. They are seeking to understand infectious pathogens, host defense mechanisms, and pathogen–host interactions and to develop therapeutic interventions. Development of vaccines is one aspect of this research. During FY 98, a scientist from China worked on a new generation of vaccines for pertussis, and an investigator from Egypt focused on hepatitis C vaccines from transgenic plants. This research was complemented by extensive collaborations with other scientists in Canada, Egypt, France, Japan, and the United Kingdom. The collaboration with Egypt was supported in part by a U.S.-Egypt Biotechnology Project Development Travel Award from FIC.

In other work, investigators from China and Israel studied the molecular biology of oral bacteria, and scientists from China, France, and the Philippines focused on the genetics of these bacteria. In studies of anthrax toxin, scientists from China, Iran, and Korea clarified the structural biology of the toxin; used fusion proteins from the toxin to induce cellular immunity to HIV; modified the protective antigen for the toxin to redirect the toxin to tumor cells; and characterized the biochemical changes that lead to toxin-induced cell death. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

In studies of autoimmunity, Chinese scientists continued their work to clone, sequence, and characterize novel genes from pancreatic islet cells. They focused on genes for IA-2 and IA-2β, two major autoantigens in insulin-dependent diabetes mellitus. Autoantibodies to these two substances appear years before the onset of clinical diabetes and are highly predictive markers for development of the disease.

Another focus of the Branch is the molecular biology of taste, smell, and pheromone reception. Investigators from China, Italy, and the United Kingdom worked to understand the mechanisms that underlie the detection and discrimination of sensory signals. In another research area, scientists from Brazil, China, France, Japan, and Korea investigated the receptors and molecular mechanisms for signal transduction in cells.

Scientists from Australia, China, and Mexico contributed to research on the mechanisms of acute and chronic inflammatory disease. They focused on the following areas: cellular and molecular mechanisms of oral tolerance in an experimental model of chronic inflammatory disease; genetic regulation of secretory leukocyte protease inhibitor—an antiviral, antibacterial, and antiproteolytic molecule; mechanisms of HIV entry into cells and potential antiviral intervention strategies; the contribution of programmed cell death (apoptosis) to the evolution of acute and chronic inflammatory disease; effects of removing TGF-β on tooth development in mutant mice; and mechanisms for administering and controlling gene therapy in experimental models of tumors and autoimmunity disease.

Under contract, an investigator at the University of Minnesota, Minneapolis, plans to collaborate with NIDR and an investigator in Burkina Faso, in an effort to characterize the mucosal immune response to HIV infection. The scientists propose to examine the role of specific and innate host factors that contribute to resistance or susceptibility to vertical retroviral transmission of HIV from pregnant women to their infants. They plan to develop and use methods and assays to explore the immunologic and viral characteristics of oral and intestinal fluids and tissues in U.S. women and of breast milk and serum in African women. Breast-feeding is encouraged in Africa but is discouraged in the United States and other industrial countries. The results of the study may provide valuable insight for the potential development of vaccines against HIV infection.

The Chief of the Branch was designated president-elect of the Society for Leukocyte Biology. A principal investigator in the Branch served on the board of directors of the Paul Ehrlich Foundation, Frankfurt, Germany. Another principal investigator served as ad hoc reviewer for several international journals and wrote a chapter for a leading British text on microbial infections, which was published during FY 98.

Oral and Pharyngeal Cancer Branch

Researchers in NIDR's Oral and Pharyngeal Cancer Branch are focusing on the molecular basis of cancer, especially the molecular events that contribute to initiation and progression of squamous cell carcinoma, the most prevalent oral cancer. Certain alterations of proteins involved in mitogenic signaling are known to exert profound effects on cellular behavior. With this knowledge, scientists from Argentina, Israel, Japan, and Spain continued to probe the normal and aberrant functioning of molecules that participate in the transduction of proliferative signals. They uncovered additional novel pathways leading to the promotion of cell growth and built on previous research, to make important discoveries about signal transduction.

Scientists from Brazil, Italy, and the United Kingdom also continued to investigate the cause, diagnosis, treatment, and prevention of oral tumors, especially squamous cell carcinoma. The objective of this research is to identify the mechanisms of neoplastic transformation in squamous cell carcinoma of the head and neck. The Chief of the Branch served as grant reviewer for several research-funding institutions in Argentina, Canada, Germany, Israel, and Italy.

During FY 98, the Branch established the Keratinocyte Biology Group. The purpose of this research group is to elucidate the mechanisms of squamous cell differentiation and the biochemical alterations that contribute to neoplastic transformation. Scientists from Argentina and Spain are contributing to this work. Using cell and molecular approaches and animal models, investigators continued to elucidate the role and mechanism of action of the p53 tumor-suppressor gene, which is inactivated in most human cancers, including those of the oral cavity. In FY 98, they issued the first report of a gene encoding a chloride channel protein that is regulated by p53 and tumor necrosis factor α pathways in keratinocytes. This finding suggests, for the first time, that this family of regulatory proteins may be involved in these pathways. In addition, the investigators clarified the contribution of the cdk inhibitor WAF1, a p53 target of transcription, to carcinogenesis in mice. The findings from these studies suggest that the WAF1 gene does not regulate malignant progression of squamous cell carcinomas and does not account for the malignancy of p53 tumors in genetically altered mice.

A researcher from Korea participated in studies of cultured keratinocytes from human oral gingival tissue. In these studies, investigators immortalized the gingival keratinocytes with plasmids containing human papillomavirus 16 and then transfected them with various oncogenes to determine which oncogene induced malignant transformation in oral epithelial cells.

Pain and Neurosensory Mechanisms Branch

NIDR's Pain and Neurosensory Mechanisms Branch conducts multidisciplinary research to improve understanding and treatment of pain. The Program integrates basic and clinical research. During FY 98, scientists from Canada, China, Israel, and Japan participated in a range of studies. They evaluated molecular responses to tissue injury and elucidated the mechanisms of inflammation of peripheral tissue, including subsequent changes within the nervous system. The scientists also evaluated new drugs and clinical hypotheses about pain and its control in human models of acute and chronic pain.

Functional Genomics Unit

Researchers in NIDR's Functional Genomics Unit study the molecular genetics of development and inflammation, focusing on functional genomics. These studies include delineation of the pathways for neuronal migration, metabolic disorders, and immune disorders such as arthritis and systemic lupus erythematosus. The researchers have genetically engineered knockout mice in which the gene for TGF-β1 is missing, to study the onset of inflammatory and autoimmune responses. During FY 98, scientists from Belgium and Japan participated in research on neuronal migration; scientists from Israel, Japan, and the United Kingdom studied Fabry's disease; and scientists from Israel and Japan analyzed the molecular aspects of inflammation.

Immunopathology Section

Scientists in NIDR's Immunopathology Section are defining the pathological effects of inflammatory processes on connective tissue. During FY 98, two scientists, from China and India, continued to contribute to these studies. The scientist from China identified specific cytokines involved in the differential regulation of matrix metalloproteinases by monocytes; examined the effect of hormone replacement therapy on regulation of monocyte functions; and delineated the role of oxidized low-density lipoprotein and peroxisomal proliferator–activated receptor in the modulation of matrix metalloproteinase production by monocytes. The scientist from India delineated specific mitogen-activated protein kinases in the signal transduction pathway for induction of phospholipase, prostaglandin H synthase-2, and matrix metalloproteinases in human monocytes. In addition, the scientist identified and characterized the regulation of monocyte membrane type 1 matrix metalloproteinase (MT1-MMP) and its relationship to activation of MMP-2 produced by bone marrow stromal and tumor cells.

Molecular Structural Biology Unit

In NIDR's Molecular Structural Biology Unit, a scientist from India studied the structure and dynamics of monomordica antiviral protein 30, a plant protein (purinase) that enters cells infected with HIV-1 and cleaves the RNA transcript at one site, thereby destroying the virus. An investigator from Japan used high-resolution nuclear magnetic resonance spectroscopy to study the structure and molecular dynamics of FAST-1, a DNA-binding protein involved in transduction of TGF-β signals. Another researcher from Japan investigated the molecular dynamics of the HIV-1 protease, both free in solution and bound to potent inhibitors of the enzyme.

XII.

National Institute of Diabetes and Digestive and Kidney Diseases

INTRODUCTION

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports both fundamental and clinical research and research training focused on several diseases characterized by chronicity and long-term disabling effects. NIDDK provides leadership for a national program in diabetes and other diseases resulting from inherited errors of metabolism, including cystic fibrosis; endocrine disorders; diseases of the gastrointestinal tract (e.g., diseases of the liver and gallbladder); diseases of the blood and bone; and kidney and urologic diseases. The Institute also conducts and supports research in nutrition and nutrition-related disorders. The major objective of this national program is to identify and pursue scientific opportunities yielding fundamental, innovative, and valuable contributions to human health.

NIDDK acquires new biomedical knowledge through grant-supported research, field studies, centrally directed collaborative research contracts, and research at NIDDK facilities in Bethesda, Maryland, and Phoenix, Arizona. The Institute's extramural programs support fundamental and clinical research conducted at universities, medical schools, and other research centers throughout the United States and abroad.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

The Laboratory of Bioorganic Chemistry is responsible for numerous scientific advances stemming from its international activities. These advances include the following:

- elucidation of the structure of biologically active alkaloids from amphibians, birds, and insects (specimens supplied by scientists in Argentina, Brazil, Chile, Costa Rica, Madagascar, Mexico, New Guinea, Panama, and Venezuela);
- illumination of routes and mechanisms of metabolism that lead to carcinogenic activity, as shown in studies of polycyclic aromatic hydrocarbons and their aza analogues (collaboration with researchers in Australia, Germany, and Northern Ireland);
- insights into structural modifications affecting activity at receptors for peptide, histamine, and adenosine triphosphate, as well as adenosine muscarinic and adrenergic receptors (cooperation with investigators in countries including Germany, Israel, Sweden, and the United Kingdom); and
- synthesis of a series of perfluoroalkylpyrimidines to be used as affinity labels for viral enzymes and for pyrimidine reductase (joint research with scientists in Japan).

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Japan

In fiscal year 1998 (FY 98), the Joint U.S.-Japan Nutrition and Metabolism Panel (formerly the U.S.-Japan Malnutrition Panel) continued its productive and cooperative efforts. The efforts were focused on obesity; endogenous mediators of nutrient metabolism; polyunsaturated fatty acids and lipid metabolism; nutritional antioxidants; and nutrition, calcium, and osteoporosis. The Conference on Cytokines, Nutrition, and the Gut was held jointly with the U.S.-Japan Panel on Cholera and Related Diarrheal Diseases, in South Carolina, in 1995. The proceedings of this conference were published in 1997 in the book *Cytokines, Cholera and the Gut,* which was coedited by the U.S. chairman of the panel, from New England Medical Center, Boston, Massachusetts, and a panel member from Omiya Medical Center, Japan. The proceedings present the results of collaborative research by U.S. and Japanese investigators focusing on the role of nutrition in human health and disease and on approaches to the study of cholera and other enteric infections.

A U.S.-Japan joint meeting and a conference entitled Nutrition and Atherosclerosis: Cellular and Molecular Mechanisms were held in Shirahama, Japan, on December 1–3, 1996. This meeting fostered significant interaction between U.S. and Japanese participants. A special feature of the meeting was the large number of junior Japanese investigators who reported on significant research findings. Their presentations were well received. During 1997, the U.S.-Japan conference on The Role of Oxidants and Antioxidant Therapy in Disease was held in Portland, Oregon, on September 25–28. The theme of the meeting was the role of oxidants and oxidant therapy in disease.

The 1997 business meeting of the panel reaffirmed the three areas of emphasis for the next 5 years: (1) obesity, diabetes, and related metabolic disorders, including dyslipidemias and atherosclerosis; (2) metabolic bone diseases; and (3) nutrition and host defense. To promote research in these areas, the U.S.-Japan Nutrition and Metabolism Panel will work to foster scientific studies directed toward a better understanding of the relationships between nutrition and disease susceptibility, progression, and outcome; genetic mechanisms at the molecular and cellular levels; and identification and investigation of new strategies for disease prevention and therapy. The panel will encourage this research in three areas—nutritional epidemiology, molecular genetics and cellular biology, and clinical studies—as they relate to emerging health problems.

Activities With International and Multinational Organizations

World Health Organization

Division of Diabetes, Endocrinology, and Metabolic Diseases

The Division of Diabetes, Endocrinology, and Metabolic Diseases, an extramural research program, is a World Health Organization (WHO) Collaborating Center for Diabetes Research, Information, and Education. The center conducts research on diabetes in representative samples of adults in the U.S. population. Data from the U.S. study are included in a compendium of studies of diabetes prevalence developed by WHO.

The Division's Diabetes Research Program supports a contract for analysis of the WHO Multinational Study for Vascular Disease and Diabetes. Morbidity and mortality for diabetes in 10 countries is the focus of this research. Goals of the study include (a) identification of risk factors and risk markers for complications and (b) quantitation of causes of interpopulation differences in microvascular and macrovascular disease in diabetes.

Phoenix Epidemiology and Clinical Research Branch

The Phoenix (Arizona) Epidemiology and Clinical Research Branch, Division of Intramural Research, continues to serve as a WHO Collaborating Center for the Design, Methodology, and Analysis of Epidemiologic and Clinical Investigations in Diabetes. This center collaborates with WHO in implementing the action program of WHO and the International Diabetes Federation, to provide advice, consultation, and collaboration for investigators. The WHO collaborating center assists (a) in development and application of study design and of standardized methods for epidemiologic and clinical investigations and (b) in analysis of data on the causes and pathogenesis of non–insulin-dependent diabetes mellitus (type 2 diabetes) and its complications. The center provides investigators with short- or long-term training experience in the methods and application of epidemiologic and clinical research on type 2 diabetes.

The center participates in the WHO Multinational Study for Vascular Disease and Diabetes, which is examining the mortality and incidence of vascular complications of diabetes among different ethnic groups in different countries.

Extramural Programs
Division of Diabetes, Endocrinology, and Metabolic Diseases

Australia

An investigator at the International Diabetes Institute, Melbourne, is evaluating the emergence of diabetes mellitus as a major chronic disease associated with social, economic, lifestyle, and environmental changes in populations in the Indian Ocean and the South Pacific. Marked differences in susceptibility to diabetes among various ethnic groups occur, and the differences have a bearing on the causes of diabetes in specific U.S. subpopulations. These longitudinal studies address (a) the contributions of specific environmental and lifestyle factors to the causes of diabetes and (b) the interactions of these factors with genetic factors that determine susceptibility to diabetes.

Canada

The University of Toronto, Ontario, and the University of Western Ontario, London, are participating in the Epidemiology of Diabetes Interventions and Complications Study—a multicenter, longitudinal epidemiologic study of the 1,441 patients who participated in the Diabetes Control and Complications Trial. This 10-year follow-up study is focusing on the development of macrovascular and microvascular disease.

Researchers at the University of Toronto are examining insulin secretion from the insulin-secreting cells (beta cells) of the pancreas. Specifically, they are attempting to elucidate the mechanism by which exocytotic proteins interact with plasma membrane ion channels. They will be using novel techniques for gene transfer to explore these interactions.

An investigator at Centre de Recherche, Hotel-dieu de Montréal, Quebec, is evaluating vanadium as a treatment for type 2 diabetes. In pilot and feasibility studies of patients with type 2 diabetes, the investigator is focusing on the efficacy of vanadyl sulfate in regulation of carbohydrate, lipid, and protein metabolism. If vanadium is safe and effective, it could reduce or eliminate the need for insulin therapy.

Investigators at the Hospital for Sick Children, Toronto, played a key role in identification of the gene responsible for cystic fibrosis (CF). These scientists are leading an international consortium that has identified more than 500 specific individual gene mutations capable of causing this clinical disorder. These investigators have identified mutations associated with pancreatic sufficiency or insufficiency, allowing physicians to predict which children with CF will require pancreatic enzyme replacement therapy. The researchers are characterizing the promoter region of the CF gene, which regulates gene expression, and have developed model systems to study the function of the protein coded for by the CF gene.

The NIDDK-supported Cystic Fibrosis Research Center, Hospital for Sick Children, Toronto, has made major strides in correlating clinical phenotype with genetic mutations underlying the disorder and in identifying a broad array of testicular defects that cause infertility in CF. In addition, these investigators are studying the role of mutations of the CF gene (CFTR) in development of idiopathic pancreatitis. These studies have greatly expanded understanding of the biological importance of the CFTR protein encoded by the CFTR gene. Roles of the CFTR protein that have been demonstrated by this study may suggest avenues for future treatment of CF, male infertility, and pancreatitis.

Under a research grant awarded to McGill University, Montreal, the role of phosphorylation in regulation of the CFTR protein is being investigated. This project addresses practical aspects of the function of the protein that would be used to improve the effectiveness of new therapies for CF.

An investigator at the Clinical Research Institute of Montreal was funded to study mechanisms for regulation of hormonal feedback. Adrenal steroid hormones such as glucocorticoids are released in response to signals from the pituitary gland that stimulate production of releasing hormone. Adrenocorticotropic hormone (ACTH) is produced in the pituitary from a large precursor complex hormone called proopiomelanocortin (POMC). The levels and extent of hormonal response are controlled by the following mechanism: when adrenal steroid levels increase above a certain amount, ACTH feeds back on the pituitary to decrease production of POMC. This research is focused on the mechanism for glucocorticoid regulation of POMC protein production by the pituitary. Study findings are expected to increase the understanding of glucocorticoid regulation of responses to stress and of inflammatory and immune responses.

China

Childhood diabetes in China is the focus of two projects in which scientists at the University of Pittsburgh, Pennsylvania, are collaborating with scientists at Beijing Hospital. In the first project, an epidemiologic study has established registries of children with diabetes who reside at different sites in China. This study will be used to define geographic, ethnic, and temporal variations in these groups. These data will be compared with data from other international childhood diabetes registries. In the second project, researchers are comparing characteristics of patients who have new onset of diabetes with characteristics in other populations, in an effort to determine whether childhood diabetes in China is associated with specific genetic alleles, immune markers, and biochemical factors.

Researchers at the Joslin Diabetes Center, Boston, Massachusetts, are collaborating with researchers at the People's Hospital, Beijing Medical University, to identify susceptibility genes involved in the development of type 2 diabetes. The investigators have obtained results suggesting that allelic variation at a particular gene locus contributes to the development of type 2 diabetes in a significant subset of families.

Denmark

Scientists at the Hagedorn Research Institute, Copenhagen, are studying the role of specific genes that code for proteins in the Notch signaling system. They are investigating how these genes contribute to regulation of endocrinogenesis of the pancreas. The purpose of the study is to determine whether in vitro modulation of the Notch system can lead to indefinite propagation of precursor pancreatic cells and whether these cells can be converted to beta cells.

Another group at the Hagedorn Research Institute is conducting research on the role of growth hormone and prolactin in the stimulation of beta cell proliferation and insulin production. The team will examine the pathways involved in the beta cell response to these hormones, with the goal of identifying and determining the function of growth hormone–regulated and prolactin-regulated beta cell genes.

Ecuador

One scientist at the University of Florida, Gainesville, and one at Stanford Medical School, Palo Alto, California, have grants for collaborative research with a group at the Institute of Endocrinology, Metabolism, and Reproduction, Quito. These scientists are studying a unique patient population that has growth hormone receptor deficiency, a syndrome characterized by marked short stature and osteopenia secondary to resistance to growth hormone. Their evaluation of the biological effects of insulin-like growth factor (IGF) in vivo includes study of bone mineral and markers of bone turnover in children with growth hormone deficiency who are beginning long-term therapy with insulin-like growth factor I (IGF-I). The effects of IGF-I treatment on growth and metabolism will be investigated.

Finland

Scientists at the National Public Health Institute, Helsinki, have been funded to establish a registry of patients with insulin-dependent diabetes mellitus (type 1 diabetes), as part of the WHO multinational registry program for type 1 diabetes. Finland has the highest prevalence of type 1 diabetes in the world, and the incidence is increasing about 1%–3% each year. These researchers are using genetic, biochemical, and environmental risk markers to determine the reasons for the high incidence of type 1 diabetes.

Israel

Investigators at the Washington University School of Medicine, St. Louis, Missouri, are seeking to clarify the genetic basis of the metabolic defects of type 2 diabetes. The focus of their studies is the Ashkenazi Jewish population in Israel, a relatively homogeneous population that makes it easier to detect genes for diabetes. Clinical and demographic data will be collected on 400 sibling pairs with type 2 diabetes, through the Diabetes Clinics at Hadassah Hospital and the Histadrut, Jerusalem. A whole-genome search will be used to identify genes that are associated with the diabetes phenotype.

Mexico

A researcher at the University of Wisconsin, Madison, is collaborating with NIDDK intramural scientists and investigators in the Nutrition Division, CIAID, Hermosillo, Sonora, Mexico, to study the causes and determinants of diabetes in a group of Pima Indians living in a remote, mountainous region of northwest Mexico. The environment and lifestyle of these Indians are strikingly different from those of the Arizona Pima Indians who have been the focus of NIDDK research for more than 30 years. Because it is believed that the two groups share a similar genetic background, this study should provide valuable information about the role of nongenetic factors in the development of diabetes.

Sweden

An investigator at the University of Washington, Seattle, is conducting a study by using a nationwide Swedish diabetes registry to define genetic, autoimmune, and viral antibody markers for type 1 diabetes in patients with disease onset at ages 15–34 years.

An investigator at Case Western Reserve University, Cleveland, Ohio, is collaborating with researchers at the Karolinska Hospital, Stockholm, to develop and apply methods for quantifying pathways of carbohydrate and lipid metabolism in humans. These studies, which use stable isotope-labeled compounds, should elucidate the role of the liver in causing hyperglycemia in patients with diabetes.

Switzerland

An investigator at the Salk Institute for Biological Studies, La Jolla, California, is collaborating with an investigator at the Institute of Pathology, University of Bern, to develop agonists and antagonists for somatostatin that can differentially affect receptor subtypes and thus affect only particular actions of somatostatin. This peptide, which is produced in the brain, inhibits the release of growth hormone and has numerous other functions as well. It is used therapeutically for the treatment of acromegaly and as an imaging tool for certain kinds of tumors. There are five subtypes of somatostatin receptors; their presence in the brain and other tissues subserves the multiple functions of somatostatin.

Multinational Studies

An international consortium has been formed to combine data from individual studies, which will be used to map genes for diabetes. Fifteen research groups from Europe and the United States have participated in a consortium to combine the data for all the genetic markers on chromosome 20. Subcontracts have been issued to groups in France, Sweden, and the United Kingdom for participation in this effort. The combined data set consists of 24 data sets, including 2 on African Americans (314 typed individuals); 13 on whites (7 on residents of the United States and 6 on residents of Europe; 4,392 typed individuals); 2 on Japanese (487 typed individuals); 6 on Mexican Americans (1,012 typed individuals); and 1 on Native Americans (1,017 typed individuals). This is the largest data set ever analyzed for a single disease.

The Diabetes Research Program supports maintenance of a colony of diabetes-prone BB rats at the University of Massachusetts, Worcester. This unique BB rat model for the study of type 1 diabetes is provided to investigators in the United States and around the world.

The Program also supports a contract at the University of Minnesota, Minneapolis, to maintain a registry of pancreas and islet transplantation, which contains data collected worldwide. This information addresses the capability of transplantation to prevent, improve, or stabilize the complications of diabetes.

Investigators at University Hospital, Boston, Massachusetts, are collaborating with researchers at the University of Montreal and at the Karolinska Institute, Stockholm, to study the role of acyl coenzyme A in insulin secretion and in type 2 diabetes and obesity. Investigators are studying an important hypothesis that has the potential of linking changes in fatty-acid metabolism that occur in obesity and type 2 diabetes to beta cell dysfunction.

The National Hormone and Pituitary Program of NIDDK supports preparation and distribution of highly purified hormones and antisera against these hormones. The hormones and antisera are provided to qualified investigators in the United States and abroad, and researchers in many countries use these products.

Division of Digestive Diseases and Nutrition

The Division of Digestive Diseases and Nutrition was the lead division in establishment of the NIDDK-NIAID (National Institute of Allergy and Infectious Diseases) International Collaboration Small Grants Program. This Program uses the small grant award mechanism to provide support for new collaborative studies that have an international component and are within the research mission of NIDDK. These grants can be awarded for clinical trials or research in the basic sciences. The NIDDK-NIAID Program takes advantage of the established collaborative activities of NIAID International Centers, in that applicants are encouraged to establish formal research collaboration with these Centers.

During FY 98, the NIDDK-NIAID Program continued to support the following projects: a clinical trial of therapy for *Helicobacter pylori* infection in Bangladesh, a study of immunity to liver infection with *Leishmania* in Brazil, and an epidemiologic investigation of the seroprevalence of hepatitis A in children in Chile.

Australia

The Liver and Biliary Diseases Program supports a joint research project at the University of California, Davis, and the Walter and Eliza Hall Institute of Medical Research, Melbourne. This collaboration is aimed at elucidation of antigen receptors in the autoimmune pathogenesis of primary biliary cirrhosis.

Bangladesh

A small, 2-year, clinical trial, entitled *H. pylori:* a Cause and Treatment Failure of Iron Deficiency Anemia, is based at the International Center for Diarrhoeal Disease Research, Dacca. The study is a prospective, randomized, double-blind, placebo-controlled trial to test the hypothesis that the poor response to iron therapy seen in iron-deficient children of Bangladesh is related to low gastric acid output caused by *H. pylori* infection. The intervention in this trial is iron therapy combined with elimination of *H. pylori* by administration of antibiotics.

Brazil

A clinical investigator at the University of Iowa, Iowa City, will determine the presence of liver-related immunosuppressive factors in human lymphocytes in patients with or without *Leishmania*. These studies will be performed in collaboration with investigators at Universidade Federal do Rio Grande do Norte, Natal.

Canada

The North American Study for the Treatment of Refractory Ascites, based at the Medical College of Virginia, Richmond, has one foreign site—Toronto Hospital. This study is a multicenter, prospective, randomized clinical trial designed to test whether transjugular intrahepatic shunt of the portal system is more effective for refractory ascites than a standard therapy—total paracentesis, sodium restriction, or diuretic agents. Refractory ascites is a serious complication of cirrhotic portal hypertension and is associated with considerable morbidity, increasing health care costs, decreasing quality of life, and eventually, death or increased risk of death after orthotopic liver transplantation.

A clinical trial on functional bowel disorders is based at the University of North Carolina, Chapel Hill, and has one foreign component at the Clarke Institute of Psychiatry, Toronto Hospital. It is hoped that this study will enroll at least 300 female patients with functional bowel disorders (irritable bowel syndrome, painful constipation, or functional abdominal pain), to access information on this complicated syndrome, which lowers quality of life and reduces individual productivity.

Chile

A clinical researcher at the University of Maryland Medical Center, Baltimore, in collaboration with the Center for Vaccine Development, Baltimore, is the principal investigator for a project that will determine the age-specific seroprevalence and seroincidence of hepatitis A infection in Santiago. In addition, the age-specific incidence of fulminant hepatic failure will be determined, to detail the incidence of fulminant hepatic failure secondary to hepatitis A infection.

China

A clinical trial, entitled Relative Effects of Diet and Exercise on Body Composition, is based in Tufts University, Boston, Massachusetts, and has two foreign sites, the Chinese Academy of Preventive Medicine, Shanghai and Beijing, China. This is a cross-sectional study of 112 healthy adult men and women, aged 37–47 years. Two hypotheses will be tested: (1) Physical activity but not dietary fat intake is a significant predictor of individual variability in total body fat. (2) The proportion of body fat located centrally is negatively associated with physical activity and not significantly associated with dietary fat intake.

Spain and United Kingdom

A clinical trial, entitled Prevention of Esophageal Varices by Beta-Adrenergic Blockers, is based at Yale University, New Haven, Connecticut, and has two foreign sites: the Royal Free Hospital, London, England, and the University of Barcelona, Spain. This clinical trial is a prospective, randomized, double-blind, placebo-controlled study designed to investigate whether early therapy with a nonselective β-adrenergic blocker can prevent or delay the development of gastroesophageal varices in patients with cirrhosis and portal hypertension.

Division of Kidney, Urologic, and Hematologic Diseases

Canada

A clinical center at Queen's University, Kingston, Ontario, is one of the major participating centers in the NIDDK-funded collaborative clinical study on chronic prostatitis. In addition to the principal investigator at Queen's University, that center includes investigators at the University of Toronto, Ontario, and the University of Calgary, Alberta. An investigator from Boston Children's Hospital, Massachusetts, who is performing genetic mapping of the zebra fish is collaborating with an investigator from Ottawa Civic Hospital, Ontario, to generate molecular reagents.

Germany

An investigator from Washington University, St. Louis, who is also performing genetic mapping of the zebra fish, is collaborating with an investigator from Max Planck Institute, Tübingen, who is providing mutant zebra fish embryos for study.

New Zealand

A scientist at the University of Auckland is studying human embryonic hemoglobin to obtain a detailed understanding of the structure and functioning of the three human embryonic hemoglobins and to gain insight into the "normal" behavior of the oxygen transport system that operates at the earliest stages of human development. Human embryonic hemoglobins will be produced in a system for expression of recombinant yeast, without recourse to use of human embryonic tissue.

Sweden

A recently funded grant addressing the mapping of genes for nephropathy in type 1 diabetes involves a major collaborative effort among investigators at the Joslin Diabetes Center, Boston, Massachusetts; the National Public Health Institute, Helsinki, Finland; and the Karolinska Institute, Stockholm.

United Kingdom

An investigator at the University of Vermont, Burlington, is collaborating with an investigator at the University of British Columbia, Vancouver, to elucidate structure–function relationships in recombinant transferrins. The results of this work are essential to understanding the molecular basis of certain defects in iron delivery and to the design of rational interventions in the delivery of iron to neoplasms.

Multinational Studies

The Division of Kidney, Urologic, and Hematologic Diseases is collaborating with the European Institute of Oncology in the study of Cancer in End-Stage Renal Disease. The Division provided data from the U.S. Renal Data System and has been taking part in this study comparing the development of cancer in patients with end-stage renal disease, in Australia and New Zealand, Europe, and the United States. A meeting was held with the research group in June 1998.

In addition, the Division collaborated in studies of patients with end-stage renal disease in Australia and New Zealand, Canada, and the United States from FY 96 through FY 98.

International Meetings

Division of Digestive Diseases and Nutrition

The Division of Digestive Diseases and Nutrition sponsored an international symposium entitled Molecular Medicine and Hemochromatosis: at the Crossroads, which was held at the National Institutes of Health, Bethesda, Maryland, on May 14–15, 1998. The meeting focused on the international and domestic issues related to identification of the hemochromatosis gene, including expression of the gene in ethnic populations and genetic screening. Invited speakers included physician-scientists from Australia, Canada, France, Italy, and the United Kingdom.

In support of efforts to elucidate alcohol-induced liver disease, the Division also cosponsored the 9th Congress of the International Society for Biomedical Research in Alcoholism, which was held in Copenhagen, Denmark, on June 27–July 2, 1998.

Division of Kidney, Urologic, and Hematologic Diseases

The Division of Kidney, Urologic, and Hematologic Diseases organized and supported an international symposium on the Biology of Prostate Growth, held in Bethesda, Maryland, in March 1998. Presenters included investigators from Asia, Australia, and Europe. Opportunities for new research strategies were developed and discussed.

In addition, the Division cofunded the International Bladder Research Conference, in San Francisco, California, in April 1998. The conference focused on basic research on the bladder and provided an excellent opportunity for investigators from many countries to exchange concepts.

The Division also organized and convened the workshop on Strategies for Identification of Nephropathy Susceptibility Genes, held in Bethesda, Maryland, on June 28–29, 1998. The meeting provided a forum for delineating the genetic predispositions underlying the pathophysiology of many genetic renal diseases, including diabetic nephropathy. Invited speakers were from Scandinavia and the United States and participants come from Italy, the Netherlands, and Scandinavia. This conference is expected to stimulate investigative interactions, so that a wider range of genetic variation can be sampled in future research on genetic predispositions to the development of kidney disease.

The Division provided partial funding for a conference of investigators who use diverse approaches for studying the integration of endothelial, epithelial, and vascular control mechanisms of the kidney. The meeting, which is convened triennially, was held at the Vermont Academy, Saxton's River, on June 26–July 2, 1998.

The Consortium of International Renal Registries met in June and October 1998 to discuss collaborative studies among the major world renal registries. These meetings are held annually, and several comparative studies are being planned, to compare incidence, prevalence, morbidity, and mortality of patients with end-stage renal disease throughout the world.

The Division supported a workshop on Ferritin Structure–Function Relationships, at Sheffield University, England, in July 1998. Experts on ferritins (the major iron-storage proteins), on related proteins, and on model systems addressed nagging questions in the literature and defined key experiments that are needed to resolve many of the problems in the field. These problems include comparability of data from different laboratories and disagreement about the site of oxidation steps; the stages leading to buildup of iron; the significance of the radicals observed in the early stages of iron oxidation; and the rates of penetration of reductants and other small molecules into the protein.

The 7th International Workshop on Developmental Nephrology was held in Stockholm, Sweden, on September 9–11, 1998. An investigator from the University of Virginia, Charlottesville, served as chairman of the organizing committee for the workshop. The meeting addressed the most recent advances in renal development.

The Division organized the Conference on Critical Issues in the Care of End-Stage Renal Disease Patients, held in Baltimore, Maryland, in September 1998.

An international conference on Iron: From Current Biochemistry to New Chelator Development Strategies was held in Bethesda, Maryland, in September 1998, and was attended by speakers and investigators from 11 foreign countries.

NIDDK provided partial support for an international conference entitled Ion Channelopathies: Hereditary Dysfunction of Ion Channels, held in Philadelphia, Pennsylvania, on October 28–31, 1998. The conference was cosponsored by the American Society of Nephrology and the International Society of Nephrology, which brought together the top biomedical scientists in the field of ion channels, along with promising young investigators and trainees, who discussed recent advances in the discovery of ion channel syndromes.

Intramural Programs and Activities

Diabetes Branch

Clinical and Cellular Biology Section

The Clinical and Cellular Biology Section collaborates with a scientist at the Institute of Histology and Embryology, University of Geneva School of Medicine, Switzerland. In this long-standing joint research effort between NIDDK and scientists in Geneva, morphological techniques have been used to investigate receptor-mediated endocytosis of insulin and related peptides.

Experimental Diabetes, Metabolism, and Nutrition Section

The Experimental Diabetes, Metabolism, and Nutrition Section is continuing collaborative studies with institutions in two countries (England and Japan) and has initiated a third study (in Sweden). In an ongoing project with the University of Bath, researchers are investigating adipose cells and skeletal muscle. A study with scientists at Yokohama City University and Tokyo University is examining the role of insulin receptor substrates in the glucose transport response to insulin and in the effect of steroid hormones on insulin action. In a new joint project at the University of Göteborg, investigators are studying components of the insulin receptor signaling pathway that regulate subcellular trafficking of glucose transporters in isolated adipose cells.

Six scientists from abroad are working in this Section: five Visiting Fellows (two from China, one from Hungary, one from Romania, and one from the United Kingdom) and one Visiting Scientist (from the United Kingdom).

Molecular Biology and Gene Regulation Section

In the Molecular Biology and Gene Regulation Section, three foreign investigators are studying the molecular biology of obesity: one Visiting Associate (from China) and two Visiting Fellows (one from China and one from Russia).

Molecular and Cellular Physiology Section

The Molecular and Cellular Physiology Section has two international studies. One study, with collaborators at the Weizmann Institute of Science, Rehovot, Israel, is focusing on the signaling pathways of IGF-I and insulin receptor. The second study involves scientists in Barcelona, Spain, and examines the role of the sulfonylurea receptor in the functions of the pancreatic beta cell and the central nervous system. Eight Visiting Fellows are working in the Section's laboratory (one from Canada, one from China, one from Colombia, two from Israel, one from Japan, and two from Spain).

Receptors and Hormone Action Section

The Receptors and Hormone Action Section is conducting one international study in collaboration with the University of Tel Aviv, Israel. The study focuses on the role of integrins in insulin signaling. In addition, the Section has one Visiting Scientist from Italy and one Visiting Associate from Turkey.

Genetics and Biochemistry Branch

The Genetics and Biochemistry Branch is host to 10 foreign scientists from six countries. There are 6 Visiting Fellows, from the Czech Republic (1), France (1), Japan (2), Slovakia (1), and Yugoslavia (1); 1 Visiting Associate and 2 Visiting Scientists from Russia; and 1 Special Volunteer from France. Work includes research in the following areas:

- a novel transcription factor found predominantly in testis;
- mechanism(s) by which the transcription factor NURR1 regulates expression of tyrosine hydroxylase;
- cloning and characterization of transcriptional regulators induced by the neural inducer noggin;
- biochemical studies of DNA mismatch repair;
- the role of chromatic structure in regulating the late steps of homologous recombination involving DNA branch migration and Holliday junction resolution;
- characterization of several recombination proteins;
- crystallization of several recombination and DNA repair proteins;
- investigation of the role of specific amino acid residues in the hydrolysis of nucleotide triphosphates; and
- identification of proteins comprising a ribonucliotide particle essential for processing of pre-rRNA (preribosomal RNA) in *Xenopus*.

Mathematical Research Branch

Scientists in the Mathematical Research Branch maintain collaborative activities with research groups in Canada and Hong Kong, China. Research groups at the University of Toronto collaborated with Branch scientists on models of synaptic transmission in the crayfish neuromuscular junction. Work with Hong Kong University of Science and Technology addresses the theory of protein folding.

During FY 98, the Branch hosted a senior sabbatical visitor from Canada. A Visiting Fellow from China is working on models of actin–myosin binding in skeletal muscle, and a Visiting Fellow from New Zealand is working on mathematical models of electrical activity and hormone secretion in hypothalamic neurons.

Metabolic Diseases Branch

Cell Regulation Section

The Cell Regulation Section has six Visiting Fellows (two from Italy and four from Japan); one Special Volunteer (from Italy and funded by Italy); and one Visiting Fellow (from Israel) who is serving a joint appointment with NIDDK and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. This Section has six collaborative projects with laboratories in Italy and Japan.

In collaboration with Italian researchers at Università degli Studi "G. D. Annunzio" Faculty of Medicine and Surgery, Palazzina Scuole di Specializzazione, Chieti, NIDDK scientists are studying the role of a 90-kilodalton immunomodulator as a protective factor in autoimmunity, cancer, and acquired immunodeficiency syndrome (AIDS). They are working on development of new drugs related to methimazole for treatment of diverse diseases such as lupus, diabetes, and rheumatoid disease. Drugs resulting from these projects have suppressed development of diabetes in the NOD mouse and of systemic lupus erythematosus in other experimental animal models. Scientists at the Center for Endocrinology and Experimental Oncology, CNR, and the Federico II Medical School, Naples, and at the Institute of Internal Medicine, Infectious Diseases, and Immunopathology, Polyclinic Hospital, Padiglione Granelli, Milan, Italy, are investigating the mechanism by which thyroglobulin acts as a transcriptional suppressor. Scientists in Milan are working to identify T cells in healthy human subjects who are able to process thyroid autoantigens to yield diverse autoimmune responses. They are working to determine which T cells are involved in response to cytotoxicity and which are involved in humoral autoimmunity.

In NIDDK-supported projects at Chiba University Medical School, Japan, investigators are exploring the mechanism by which thyroid-stimulating hormone (TSH), insulin, and IGF-I control thyroid cell growth through 3-hydroxy-3-methylglutaryl coenzyme A reductase and small G proteins. They have determined the role of TSH-induced geranylation in signaling the onset of growth in thyroid cells. Investigators studying the mechanism for development of thyroid autoimmune disease have uncovered a new experimental model of Graves' disease and, for the first time, have defined the role of aberrant expression of major histocompatibility genes in development of thyroid autoimmunity. They have also identified TSH receptor epitopes important for both the development and expression of autoantibodies to the thyrotropin receptor in thyroid autoimmune diseases.

Genetics and Endocrinology Section

The Genetics and Endocrinology Section has one Special Volunteer from Brazil (funded by Brazil), one Visiting Scientist from Germany, and one Visiting Associate from India. An investigator from the Section lectured at the 1st International Symposium on Molecular Genetics in Endocrinology, in São Paulo, Brazil, on December 5–7, 1997, and at the International Congress on Hereditary Cancer Diseases, in Düsseldorf, Germany, on August 26–28, 1998. A collaborative study with the University of Würzburg, Germany, led to new findings about chromosome 11 in benign and malignant adrenal tumors and the rarity of gene mutation in multiple endocrine neoplasia type 1.

Kidney Diseases Section

The Kidney Diseases Section conducts research on the pathogenesis and treatment of glomerular diseases, especially lupus nephritis, membranous nephropathy, focal glomerulosclerosis, and nephropathy associated with human immunodeficiency virus (HIV). Six scientists from five countries worked on these projects during 1997: two Visiting Fellows (one from China and one from Hungary); one Visiting Associate (from Thailand); and three Special Volunteers (one from Argentina and two from Japan).

Molecular Pathophysiology Section

The Molecular Pathophysiology Section is host to four Visiting Fellows (one from Canada, one from China, one from Russia, and one from Turkey). These scientists are studying disorders of signal transduction. The Section, in conjunction with the National Institute of Dental Research, is developing an international consortium, which will include Europe and Israel, for the study of patients with fibrous dysplasia of bone and McCune-Albright syndrome.

Molecular and Cellular Endocrinology Branch

In FY 98, the Molecular and Cellular Endocrinology Branch had 14 investigators from six countries and Taiwan working in the laboratory. These investigators were from Australia (2), China (5), India (2), Japan (2), Korea (1), Malaysia (1), and Taiwan (1). The Branch continues to collaborate with two institutions in two countries: Justus-Liebig University, Giessen, Germany, and Nagoya University, Japan.

Molecular and Clinical Hematology Branch

The Molecular and Clinical Hematology Branch has active collaborative studies with investigators from two countries, China and Thailand. The response of patients with thalassemia major and other genetic hemoglobin diseases to hydroxyurea, erythropoietin, and other drugs is the subject of joint studies with two Chinese institutions: Shanghai Institute of Medical Genetics and the Shanghai Children's Hospital.

Laboratory of Biochemistry and Genetics

Genetics of Simple Eukaryotes Section

The Genetics of Simple Eukaryotes Section is hosting three Postdoctoral Fellows from two countries (two from France and one from the Netherlands). The investigators from France are studying the mechanism by which the protein product of the SKI gene of yeast is able to block viral replication. They also are defining the parts of the Ure2p prion protein that are involved in stabilizing the normal structure or promoting conversion to the prion form. The researcher from the Netherlands is examining the MAK21 protein and its roles in ribosome biogenesis and in viral propagation.

Morphogenesis Section

The Morphogenesis Section supports the following international research activities: a joint study with the University of Amsterdam, the Netherlands, on cross-links in the yeast cell wall and a collaborative project with the University of Salamanca, Spain, on structure–function relationships in yeast chitin synthetases.

Laboratory of Biochemistry and Metabolism

The Laboratory of Biochemistry and Metabolism has nine Visiting Fellows from five countries and Taiwan. The investigators are from Canada (one), China (four), Germany (one), Russia (one), the United Kingdom (one), and Taiwan (one). The Laboratory has two collaborative studies. The interrelationship between hepatitis B virus and hepatocellular carcinoma is being explored in collaboration with investigators at the Institute of Technology, Beijing, China, and research on generation of a mouse model for achondroplasia is being successfully concluded with investigators at the Weizmann Institute of Science, Rehovot, Israel.

Laboratory of Bioorganic Chemistry

The Laboratory of Bioorganic Chemistry continues to be a leader in the fields of biochemical pharmacology and medicinal chemistry, because of its constant innovations and introduction of new concepts and agents. Scientists from many nations work in the Laboratory, which collaborates with scientists from institutions and universities around the world. Through these international research efforts, new natural products with potentially useful biological activities have been identified and are being used worldwide in studies of the roles of ion channels and second messengers in the function of numerous physiological systems. These natural products include the following:

- forskolin, an activator of adenylate cyclase;
- batrachotoxin, an activator of sodium channels;
- histrionicotoxin, a noncompetitive blocker of nicotinic receptor–regulated channels;
- pumiliotoxin, a potent myotonic and cardiotonic agent;
- epibatidine, a nicotinic agonist that is many times more potent than morphine as an analgesic agent;
- maitoxin, a potent activator of calcium influx and phosphoinositide breakdown; and
- ibogaine, an extremely potent noncompetitive blocker of ganglionic and neuronal nicotinic receptors.

Through collaborative efforts in Costa Rica, Panama, and Venezuela, insects have been identified as dietary sources for some of the biologically active alkaloids found in the skin of frogs. Alkaloids were also discovered in the skin and feathers of certain birds from New Mexico and Papua New Guinea. In addition, structures of new biologically active natural products from plants and marine organisms from New Zealand were determined.

Many of the international research efforts have involved programs (a) for discovery of new natural and synthetic compounds and their evaluation as antiviral agents or as agents for treatment of cardiovascular disease or diseases of the central nervous system and (b) for evaluation of the activity of adenosine, adenosine triphosphate, peptide, histamine, dopamine, serotonin, and cholinergic and adrenergic receptors. These collaborative studies have led to development of new synthetic routes for preparation of novel analogues of biologically active substances and novel techniques for determination of post-translational modifications of proteins.

During most of FY 98, the Laboratory of Bioorganic Chemistry consisted of four sections (Drug–Receptor Interactions, Molecular Recognition, Molecular Signaling, and Pharmodynamics) and three work groups (Neuroscience, Mass Spectrometry, and Nuclear Magnetic Resonance Spectroscopy). The Laboratory continues to have major international commitments, both with foreign scientists who are training in the Laboratory and through collaboration with scientists in many countries. Scientists from Canada, China, Germany, Israel, Italy, Japan, Korea, New Zealand, and Vietnam are receiving postdoctoral training in the Laboratory.

Numerous scientific advances stem from the international activities of the Laboratory of Bioorganic Chemistry. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.") Current and continuing collaborative efforts with foreign countries include the following:

- Argentina—with the University of Buenos Aires on studies of biologically active alkaloids from Argentinean toads and dietary arthopods.
- Australia—with the Pharmaceutical Research Institute, Queensland, on novel nicotinic agonists from endemic plants; with the University of Adelaide on dietary origin of alkaloids from myobatrachid frogs; and with the University of Sydney on studies of metabolism and tumorigenicity of benzacridines and the mechanism of action of human epoxide hydrolase.
- Brazil—with Universidade Federal Rio de Janeiro on discovery and investigation of biologically active products.
- Canada—with the University of Western Ontario, London, on development of xanthines for improvement of tolerance to cold; with the Montreal Research Institute on evaluation of analogues of opioid peptides in the central nervous system; with the University of British Columbia, Vancouver, on xanthines as inhibitors of mitosis; and with the University of Calgary, Alberta, on involvement of excitotoxic mechanisms in neuronal death caused by neurovirulent strains of HIV macrophages.
- Chile—with the University of Chile, Santiago, on the effects of pumiliotoxin on ryanodine receptors.
- Germany—with the Free University of Berlin on genetic analysis of G protein–coupled receptors; with the University of Mainz on mechanisms of polycyclic aromatic hydrocarbon–elicited carcinogens; with the University of Münster on stereoselective syntheses of fluorinated dihydroxyphenylserines; and with the University of Frankfurt on inhibition of ectonucleotidases.
- Israel—with Haifa University, on thio analogues of ultimate carcinogens from polycyclic aromatic hydrocarbons; with the Institute for Biological Research, Nes Ziyyona, on molecular probes for cholinergic receptors; and with Bar-Ilan University,

Ramat Gan, on the development of novel systems for drug delivery and the action of adenosine agonists and antagonists on cardiac myocytes.

- Italy—with the University of Bari on renal effects of adenosine receptor agonists and antagonists; with the University of Ferrara on the design of selective adenosine agonists; with the University of Milan on second-messenger systems associated with purinoceptors and on mechanisms of apoptosis induced by adenosine; with the University of Parma on the biological activity of histamine analogues; and with the University of Rome on investigation of biologically active alkaloids and amines from amphibians.
- Japan—with Osaka City University on isolation and elucidation of the structure of alkaloids from amphibians; with Kumamoto University on the development of affinity labels for receptors and ion channels; with Tohoku University and the University of Tokyo on structural and biological activity of marine toxins; with the National Research Institute, Nagoya, on perfluoroalkylation of aromatic and heterocyclic rings; with Nagoya City University on metabolism of polycyclic aromatic hydrocarbons; with Toyama Medical and Pharmaceutical University on enantio-selective electrophilic fluorination; with Gifu University on the use of cytokine knockout mice in research on dementia secondary to AIDS; and with Tokushima Bunri University, on the synthesis of fluorinated chalcones as potential inhibitors of 5-lipoxygenase and cyclooxygenase.
- Korea—with the Korea Advanced Institute of Science and Technology, Taejon, on the structure of tetrodotoxin analogues from amphibians.
- Madagascar—with Service de Chimie on investigation of biologically active alkaloids from amphibians and arthropods.
- Mexico—with Universidad de Mexico, Mexico City, on centrally active alkaloids from birds.
- the Netherlands—with the Academic Medical Center, Amsterdam, on pathogenesis of hepatic encephalopathy, and with the Center for Biopharmaceutical Sciences, Leiden, on molecular modeling and site-directed mutagenesis of purinergic receptors and on pharmacokinetics of adenosine receptor ligands.
- New Zealand—with the University of Canterbury on the identification of biologically active compounds from natural products.
- Northern Ireland—with Queens University of Belfast on synthesis of optically active arene oxides.
- Panama—with the Smithsonian Tropical Research Institute, Panama City, on insect origins for biologically active alkaloids in skin of certain neotropical frogs.
- Portugal—with the Gulbenkian Institute, Lisbon, on biological activity of xanthines in neuromuscular preparations.
- Sweden—with the Karolinska Institute, Stockholm, on evaluation of purine nucleosides and nucleotides, the biological activity of caffeine and related xanthines, and the biological activity of adenosine analogues, and with Uppsala University on synthetic incorporation of fluorinated purines and pyrimidines into polynucleotides and on studies of the biological activities of these analogues.
- Thailand—with Kasetsart University, Bangkok, on identification, structure, and biological activity of natural products.
- Turkey—with the University of Ankara on involvement of oleic amide in manifestations of hepatic encephalopathy.
- United Kingdom—with University College, London, England, on evaluation of adenosine triphosphate analogues and purine antagonists; with the University of Manchester, England, on evaluation of neuropeptide hormone analogues in the cardiovascular system and the central nervous system; with the University of Nottingham, England, on electrophysiological effects of antibodies to the AMPA receptor elaborated during the course of HIV infection; with Kings College, London, and Victoria Hospital, Newcastle upon Tyne, England, on mechanisms of pathogenesis of hepatic encephalopathy; and with the University of Dundee, Scotland, on immunohistochemical localization of protein kinase C isozymes in transfected cells.
- Venezuela—with Internacional Instituto de Estudios Advancados on investigation of effects of toxins on ion channel function.

Laboratory of Cell Biochemistry and Biology

The Laboratory of Cell Biochemistry and Biology is hosting five investigators from four countries: one Visiting Scientist (from Hungary); two Visiting Fellows (one from Germany and one from Italy); and two Special Volunteers (one from China and one from Italy). The Laboratory is involved in eight studies with investigators in seven countries: Canada, China, France, Hungary, Italy, Japan, and the United Kingdom.

Cell Biochemistry Section

The Cell Biochemistry Section is collaborating on studies of the structural characteristics of nuclear proteins with an investigator at the Medical Research Center, Cambridge, England.

Lipid Cell Biology Section

The Lipid Cell Biology Section supports four international research activities. Collaboration with a Canadian investigator at the Royal Victoria Hospital, Montreal, focuses on lipoprotein metabolism. Genetic diseases of cholesterol metabolism are the subject of the joint work with a scientist at the Faculté de Médecine, Lyon, France. Two Japanese collaborative efforts, one with the Ehime University and one with the Nippon Medical School, Tokyo, involve imaging studies of adipocytes and cultured blood cells.

Laboratory of Cellular and Developmental Biology

The Laboratory of Cellular and Developmental Biology is host to 19 international researchers.

Developmental Biochemistry Section

In the Developmental Biochemistry Section, two Visiting Fellows (one from Australia and one from China) are investigating the developmental genetics of germline sex determination in *Drosophila melanogaster.* A tenure-track Senior Staff Scientist (from the United Kingdom) has established a research group with two Visiting Fellows (one from Canada and one China) who are using minichromosomes in *Saccharomyces cerevisiae* to study the activation of gene expression. In the Unit, one Visiting Fellow (from India) is investigating the optimization of large-scale expression systems for clinically relevant proteins. One Visiting Fellow from Slovakia is studying sequence-directed protein folding, by using site-directed mutagenesis in bacteria.

Mammalian Developmental Biology Section

In the Mammalian Developmental Biology Section, two Visiting Fellows (one from Canada and one from China), one Staff Fellow (from Italy), and one Special Volunteer (from Japan) are investigating the molecular basis of female gonadogenesis, mechanisms of oocyte-specific gene expression, and the structural basis of species-specific fertilization.

Membrane Regulation Section

In the Membrane Regulation Section, two Visiting Fellows (from China) and two Special Volunteers (one from France and one from Japan) are investigating the role of intrinsic lipid proteins in the formation and hydrolysis of neutral lipid-storage droplets. In addition, one Visiting Fellow from China is studying enhancer-dependent expression of globin genes in K562 cells.

Molecular Mechanisms of Development Section

In the Molecular Mechanisms of Development Section, three Visiting Fellows (two from China and one from Korea) and one Visiting Associate (from China) are investigating the role of signal transduction in controlling pattern formation and cell fate in *Dictyostelium discoideum.*

Laboratory of Chemical Biology

The Laboratory of Chemical Biology is hosting six Visiting Fellows, one from each of six countries: Albania, China, Jamaica, Poland, Russia, and Turkey. These scientists are supported primarily by the Visiting Fellow Program and the Intramural Research Training Award. Two of these scientists are conducting research on the control of globin gene expression; two are studying the use of adenovirus-associated vectors for gene transfer; and two are conducting individual studies on the culture of human erythroid cells and the treatment of patients with thalassemia.

The Laboratory has active collaborative studies with investigators from six countries: France, Greece, Israel, Japan, Korea, and Macedonia. A continuing research effort with French scientists at Hôpital Necker, Hôpital Tenon, and Hôpital Robert Debré is part of the Parisian Prospective Study of Sickle Cell Disease. The Laboratory helped to initiate this study, which is monitoring the progression of symptoms in virtually all newborn babies with sickle cell disease in the Paris region.

The Laboratory initiated a formal research collaboration in the U.S.-Macedonian Scientific Exchange Program, with investigators at the Macedonian Academy of Science and Arts, Skopje, on aspects of the genetic hemoglobin diseases.

Laboratory scientists continue to collaborate with scientists at the Pusan University Medical School, Korea, in investigations of aspects of the control of expression of the globin gene. Related studies continue with investigators at the University of Athens School of Medicine, Greece; Hadassah Medical School, Tel Aviv, Israel; Nippon University, Tokyo, Japan; and Mahidol University, Bangkok, Thailand.

Laboratory of Genetics and Physiology

The Laboratory of Genetics and Physiology has nine Visiting Fellows from five countries: England (one), Germany (two), Japan (three), Russia (two), and Spain (one). The Laboratory has two collaborative studies with France—a study to provide information on the role of the prolactin receptor in mammary gland development and tumorigenesis and a study to provide information on the DNA-binding specificity of the transcription factors Stat5a and Stat5b. In addition, the Laboratory is conducting a joint study with Germany, to provide information on the role of the Janus tyrosine kinase 2 (JAK2) gene in mammary gland development.

Laboratory of Medicinal Chemistry

The Laboratory of Medicinal Chemistry hosted 12 scientists from seven countries and Taiwan. These scientists consisted of 7 Visiting Fellows (3 from China, 1 from Germany, 1 from Ukraine, 1 from the United Kingdom, and 1 from Taiwan); 1 Visiting Associate from China; 3 Special Volunteers (1 from Canada, 1 from Japan, and 1 from Ukraine); and 1 Visiting Scientist from Russia.

Section on Biomedical Chemistry

The Section on Biomedical Chemistry continues to have two major collaborative efforts. The first study, with the University of Leiden, the Netherlands, involves the synthesis and biological activities of 2-5A-peptide nucleic acids. This research has resulted in one report that will be published soon in *Bioorganic Biomedical Chemistry* and one patent application. The second study, with Gifu University, Japan, involves the preparation and measurement of biological activities of analogues of 2,5-oligoadenylates.

The Section hosts three Visiting Scientists (one from Canada, one from China, and one from Germany).

Section on Carbohydrates

The Section on Carbohydrates has two Visiting Fellows from China. They are involved (1) in mapping the interaction of *Vibrio cholerae* antigens and their homologous antibodies and (2) in design, synthesis, and analysis of conjugate vaccines against cholera.

The Section has one Cooperative Research and Development Agreement with Croatia, for work on development of compounds that enhance the immune response. The vehicle for this study is a polysaccharide from *Cryptococcus neoformans,* a fungus that seriously threatens immunocompromised patients.

In addition, researchers in the Section have been engaged in collaborative work with scientists at the Slovak Academy of Sciences, Bratislava, Slovakia, to prepare reagents that can localize and identify polysaccharides in plant or mammalian tissues.

Drug Design and Synthesis Section

In the Drug Design and Synthesis Section, an Intramural Research Training Award Fellow from China examined structure–activity relationships of ligands that interact with the dopamine transporter site. These agents have the potential to block the physiological response of animals to cocaine.

The Section is also involved in work with investigators from the Polish Academy of Sciences in a program designed to gain further insight into the mechanism of action of cocaine and other stimulant drugs in the central nervous system. A Special Volunteer from a Japanese pharmaceutical company was involved in various aspects of this work aimed at deciphering the requirements for ligand interaction with G protein–coupled opioid receptors. A Visiting Fellow and a Special Volunteer from Ukraine synthesized potentially valuable enantio-selective ligands and potent ligands for the δ opioid receptor. This receptor system is known to be involved in the analgesic process, perhaps without interaction with respiratory centers and without involvement of areas in the central nervous system that induce tolerance and dependence. The δ opioid ligands may also be capable of blocking response to cocaine. A Visiting Fellow from the United Kingdom is studying the structural changes necessary to convert μ receptor–selective opioids to δ receptor–selective agonists and antagonists. A Visiting Fellow from Taiwan synthesized iodo and fluoro derivatives of a corticotropin-releasing hormone antagonist as potential imaging agents for SPECT studies and positron emission tomography scans, respectively.

In addition, the Unit of Receptor Biochemistry and Pharmacology has a Visiting Scientist from Russia and is involved in collaborative work on σ receptor mechanisms with investigators at Hadassah Medical School, Hebrew University, Jerusalem, Israel. This project is aimed at determining the role of & receptors in regulation of intracellular calcium and the possible use of calcium as a second messenger. Furthermore, the role of σ receptors in regulation of cell growth and induction of apoptosis is being studied. An ongoing joint effort with a group from the Institute for Pharmaceutical Chemistry, University of Vienna, Austria, involves studies of the structure and activity of σ ligand. This project is aimed at determining the effect of various azole and aminoazole systems on σ receptor binding affinity. The research will involve quantitative molecular modeling techniques to devise a pharmacophoric model predictive of ligand affinity at σ receptors.

Collaborative work continues with researchers at the Centre Hospitalier, Universitaire de Bicetre, Assistance Publique Hôpitaux de Paris, France. The purpose is to investigate the role of a novel, haloperidol-insensitive σ binding site in modulation of NMDA receptors by σ ligands.

Laboratory of Molecular Biology

The Laboratory of Molecular Biology continued extensive collaboration with 12 institutions in 10 countries. The scientists were from Belgium (one), Canada (one), China (one), the Czech Republic (one), Germany (one), India (one), Italy (one), Korea (one), Sweden (one), and the United Kingdom (three).

Twenty-six investigators from 15 countries worked with scientists in the Laboratory at some time in 1998. This group of investigators consisted of 1 Visiting Scientist from Israel; 1 Staff Scientist from Malta; and 24 Visiting Fellows from 14 countries: Austria (1), Belgium (1), Canada (4), China (3), France (2), India (1), Ireland (1), Israel (1), Japan (2), Korea (3), Mexico (1), the Philippines (1), Portugal (1), and the United Kingdom (2).

Laboratory of Molecular and Cellular Biology

Cell Growth and Differentiation Section

The Cell Growth and Differentiation Section hosted three Visiting Fellows (one from Canada and two from Japan) and one Guest Scientist (from Japan). These researchers have been working on the elucidation of molecular mechanisms involved in tissue-specific hormone-dependent expression of the milk protein gene in the mammary gland. Their research also included investigation of the regulation of the prolactin receptor and its signal transduction mechanism.

Staff in the Section work with researchers at the University of Chile, Santiago, to investigate the role of growth factors in mammary gland development. This Section also collaborates in a study with scientists at the Shimane Medical University, Japan, to study the regulation and function of purinergic receptors in the mammary gland.

Section on Genomic Structure and Function

The Section on Genomic Structure and Function continues its collaboration with an investigator at the Institute of Science of Evolution, University of Montpellier II, France, on study of the evolutionary dynamics of the L1 family of mammalian transposable elements and on the development of a novel approach to phylogenetic analysis based on L1 amplification events. The French government has participated by funding a Postdoctoral Fellow, who worked in the Laboratory of Molecular and Cellular Biology in FY 95. In addition, the Laboratory is providing a Fogarty Fellowship for another French scientist for 1998. The Section hosted a Visiting Fellow from South Africa who worked on the DNA structure of hypervariable regions.

Steroid Hormones Section

The Steroid Hormones Section hosted two Visiting Associates (one from Belgium and one from India), one Visiting Clinical Associate (from Greece), and one Visiting Fellow (from Russia). The Visiting Associate from Belgium has been studying the modulation of glucocorticoid-regulated gene expression. The Visiting Clinical Associate from Greece has been comparing two mechanisms for modifying glucocorticoid-regulated gene expression. The Visiting Associate from India has been cloning some of the novel *trans*-acting factors that are thought to be involved in the modulation of glucocorticoid-regulated expression. The Russian Visiting Fellow has examined the ability of *trans*-acting factors to modify the DNA binding of steroid receptors.

Investigators in the Steroid Hormones Section are collaborating with scientists at the University of Fribourg, Switzerland, to examine the effect of selected point mutations on receptor function.

XIII.
National Institute on Drug Abuse

INTRODUCTION

It is the mission of the National Institute on Drug Abuse (NIDA) to lead the Nation in bringing the power of science to bear on drug abuse and addiction. The two critical components of this charge are (1) the strategic support and conduct of research across a broad range of disciplines and (2) the rapid and effective dissemination and application of the results of that research to significantly improve prevention, treatment, and policy in relation to drug abuse and addiction.

The international program implements the NIDA mission through coordination with international and regional organizations, with other agencies of the U.S. Government, and with nongovernmental organizations involved in research on drug abuse and related health consequences. Through the International Visiting Scientists and Technical Exchange (INVEST) Program, NIDA fosters international research collaboration through technical consultation, scientific exchange, information dissemination and international communications networks, and research fellowships.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Brazil

In fiscal year 1998 (FY 98), researchers at the University of Miami, Florida, and Brazilian community-based researchers completed the 5th year of the project HIV/AIDS Community Outreach (PROVIVA), in Rio de Janeiro. This prevention intervention project is part of NIDA's Cooperative Agreement for AIDS Community-Based Outreach–Intervention Research. The initiative includes 23 sites from Alaska to Florida and from Puerto Rico to Brazil. The general objectives of the research were

1. to establish a community surveillance and monitoring system in Rio de Janeiro, for human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS);
2. to develop, implement, and evaluate a community-based HIV/AIDS prevention intervention program for cocaine injectors and snorters and for male transvestite sex workers in the city's shantytowns, red-light (prostitution) districts, and other neighborhoods where rates of drug use on the street are high; and
3. to pilot an effective field-based HIV prevention program that could be used in other communities in Brazil and throughout Latin America.

Four findings and outcomes of this research project were especially significant. First, there were statistically significant reductions in HIV risk behaviors. Both cocaine injectors and cocaine snorters reduced the number of days they had used drugs and the number of times they had used cocaine in the previous 30 days.

Second, after recruitment and follow-up ended in the fall of 1997, ethnographic fieldwork continued. The fieldwork indicated that the project had been a success. For most of the clients, this had been the first time they had participated in an HIV intervention program.

Third, the investigators conducted focus groups with health care workers in several parts of Brazil in an effort to make the intervention protocol more culturally appropriate for use throughout Brazil. They also discussed the project with Brazilian scientists to facilitate diffusion of innovation and to stimulate replication of the NIDA-funded research.

Fourth, the Brazilian Ministry of Health has adopted the intervention as a national model for preventing HIV/AIDS among drug users.

Canada

In a study of the Neurobiology of Relapse Induced by Stress and Drugs, a NIDA-funded researcher at Concordia University, Montreal, Quebec, is examining factors involved in relapse behavior of rats during reinstatement of heroin and cocaine by injection. Microdialysis will be used to assess the neuronal adaptations that may account for susceptibility to stress-induced relapse after previous long-term exposure to drugs.

A researcher at the Addiction Research Foundation, Toronto, Ontario, is exploring the roles of the cholinergic and opiatergic neurotransmitter systems in the regulation of mesolimbic dopamine neurons in drug reinforcement. Midbrain dopaminergic cells are thought to have a critical role in reward processes and to mediate many of the effects of drugs of abuse. This investigator was one of the first to successfully develop an animal model to reliably study self-administration of nicotine in rats and has already shown that nicotine activates dopamine projection neurons by mechanisms similar to those of cocaine. Two hypotheses are being tested: (1) that drug reinforcement is influenced by cholinergic projections to the ventral tegmental area from the pedunculopontine tegmental and laterodorsal tegmental nuclei and (2) that populations of μ-type opiate receptors, which are also located in the pedunculopontine nucleus, are strategically placed to modulate mesolimbic dopamine cells and to influence self-administration of cocaine.

Colombia

A prospective longitudinal study of a sample of Colombian youth (adolescents at study entry) and their parents was in its 3rd year in FY 98. Researchers at Mt. Sinai School of Medicine, New York City, New York, and Universidad de Antioquia, Medellín, are examining the causes of changes and patterns in adolescent drug use, other problem behaviors, and the consequences of drug use on the individual and his or her family. This longitudinal study is investigating interrelationships and interactions of personality, family, peers, ecological context, drug context, and cultural factors, as they affect the course of drug use, delinquency, precocious sexual behavior, and specific behaviors that increase the risk of AIDS.

Dominican Republic

In FY 98, NIDA awarded an administrative supplement to the National Development and Research Institutes, New York City, New York, and Profamilia, Santo Domingo, to conduct an exploratory qualitative study of high-risk drug users in the Dominican Republic. Drug use and HIV/AIDS are serious and growing concerns in that country. A significant number of people migrate each year from the Dominican Republic to the New York City metropolitan area and to Puerto Rico. In light of these concerns, there is a need to determine whether it is feasible to conduct cross-cultural research in the three locations, with persons from the Dominican Republic who are at high risk for HIV/AIDS. The overall goal of the project is to identify and describe populations that use heroin, cocaine, or both, particularly in terms of behaviors related to drug use and sexual activity that increase HIV risk. The aims of the study in the Dominican Republic are (1) to identify and compile information that characterizes populations using heroin, cocaine, or both; (2) to develop methods to access these populations for interviews; (3) to collect pilot qualitative data to explore determinants of HIV risk behaviors and identify patterns of travel and migration to New York City and Puerto Rico; and (4) to reinforce institutional capacity in the Dominican Republic for study of the relationship between drug abuse and HIV/AIDS. Research activities related to each of these aims are now under way, with the expectation that study results and recommendations for future research in the Dominican Republic will be available in the spring of 1999.

The Netherlands

Scientists in the Department of Medicinal Chemistry, University Centre of Pharmacy, Groningen, and the NIDA Intramural Research Program discovered a potential neural trigger for schizophrenia and a new atypical antipsychotic drug. Work also continues on the role of neuroactive steroids in drug dependence and on toxic effects related to drug abuse.

Russia

Researchers from the Center of Chemistry of Drugs, Russian Ministry of Public Health, Moscow, and NIDA's Intramural Research Program collaborated to characterize the preclinical pharmacology of a novel stimulant, mesocarbe (Sydnocarb), for possible use in treatment for abuse of psychomotor stimulants.

Venezuela

A research study by the National Development and Research Institutes, New York City, which was in its 2nd year in FY 98, seeks to identify a model to explain vulnerability to drug use among adolescents in two Hispanic cultures. The scientists are using both qualitative and quantitative approaches and are incorporating a multidimensional perspective that integrates mainstream and subcultural theories. The purposes of the project are (1) to apply a qualitative approach through ethnographic field research, which will identify culturally relevant categories of risk and protective factors and describe the linkages between these categories; (2) to develop a culturally sensitive and relevant instrument for assessment of risk and protective factors in the two Hispanic samples; (3) to develop a culturally valid and well-fitting model for prediction of drug use among Puerto Rican-American and Venezuelan youth; and (4) to advance a cross-cultural program for joint research by the United States and Latin America, focusing on adolescent drug abuse. The investigators are conducting in-depth ethnographic interviews of adolescents in Newark, New Jersey, and Caracas, Venezuela, who are receiving treatment for substance abuse and of adolescents in the communities of East Harlem and East New York, in the United States, and Caracas, Petare, and Catio, in Venezuela. Support was provided for development of the assessment instrument and for a pilot study, in preparation for formal administration of the instrument to Hispanic adolescents in the two countries.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

China

A NIDA-funded researcher at Beijing Medical University is continuing to perform research on acupuncture, pain, and drug addiction. The first series of studies explored the ability of electroacupuncture to reduce pain in models of chronic pain in rats. These models included pain from crushed nerves and nerve inflammation. In other studies, the researcher is examining the role of the opioid-like peptide orphanin FQ in analgesia and pain tolerance induced by electroacupuncture. The broad range of research techniques includes use of knockout mice, immunocytochemistry, radioimmunoassays, and patch clamp methods for examining channel conductance.

France

A research report describing results of a long-term international study by an investigator in NIDA's Intramural Research Program and an investigator at Institut National de la Santé et de la Recherche Médicale was published in *Neuroscience,* in 1998. The findings indicate a potential for use of a σ receptor ligand (PRE-084) as an antiamnesic agent against mnemonic impairment induced by the central injection of B25-35-amyloid peptide, which is the core component of the senile plaque found in the brain of patients with Alzheimer's disease. PRE-084 was discovered by scientists in the NIDA Intramural Research Program. The collaboration between these two investigators started in 1994, when they first published a report describing the beneficial effect of PRE-084 against the memory loss induced by the phencyclidine-like drug, dizocilpine (MK-801), and by the nicotinic acetylcholine antagonist mecamylamine *(Pharmacology, Biochemistry, and Behavior,* December 1994). Since then, the investigators have found that PRE-084 also blocks memory loss induced by the L-type calcium channel blocker nimodipine (*Journal of Neural Transmission,* 1995) and memory loss observed in genetically senescence-accelerated mice (*Brain Research,* 1996). As σ receptors are implicated in learning and memory and in certain psychiatric disorders such as depression and drug abuse, this international collaboration will continue to contribute significantly to understanding of the basic mechanisms underlying the action of this important receptor system.

Russia

Under a U.S. Civilian Research and Development Foundation award, scientists in the NIDA Intramural Research Program and at the State Research Center of Addictions, Moscow, continue to collaborate to develop new compounds for treatment of opiate addiction. In FY 98, they studied participation of nonopioid peptides (substance P, diazepam-binding inhibitor fragment, and neuropeptide Y) in the mechanisms underlying genetic predisposition to high anxiety in strains of rats with or without a high level of anxiety, as measured in several stressful situations. Preliminary findings suggest (a) that decreased levels of substance P in some regions of the brain (e.g., hippocampus, midbrain, and hypothalamus) may lead to a high level of anxiety in rats; (b) that decreased levels of diazepam-binding inhibitor fragment and increased levels of neuropeptide Y in animals with high anxiety may act as compensatory mechanisms; and (c) that differences in the levels of these peptides in different brain areas may modulate sensitivity to the activity of morphine.

Multicountry Projects

A NIDA-funded researcher at Harvard University, Boston, Massachusetts, is collaborating with researchers from around the world to gather existing data sets from population-based surveys that used the Composite International Diagnostic Interview (CIDI). This effort is resulting in a unique multicountry, merged data set that provides an unprecedented opportunity for cross-national comparison of the patterns, predictors, and consequences of substance use and disorders of substance use. It is estimated that the final merged data set will include survey data from 13 countries. Initial analyses focused on populations in Canada, Mexico, and the United States and were conducted with researchers at California State University, Fresno; the Mexican Institute of Psychiatry, Mexico City; and McMaster University, London, Ontario.

A NIDA-funded researcher at Washington University, St. Louis, Missouri, is analyzing data from general population surveys that used comparable data collection instruments, in Canada, Korea, New Zealand, the United States, and Taiwan. The purpose of the analyses is to examine pathways from problems in childhood behavior and conduct to adult substance abuse. The researcher is investigating cross-societal differences in (1) associations between the severity, syndrome, and age at onset of conduct problems, and substance abuse and adult psychopathology and (2) demographic cofactors and mediating or preceding psychopathologic conditions related to these associations.

A NIDA-funded researcher at the University of California, Santa Cruz, is collaborating with independently funded investigators in Bremen, Germany, and Amsterdam, the Netherlands, to examine the course of marijuana use by persons in San Francisco, Bremen, and Amsterdam. The three studies are using comparable sampling strategies and data collection instruments. Results of comparative analyses are expected to contribute to understanding of the influence of the psychological sets of users, social settings of use, and sociocultural variables and differences in legal policy on patterns of marijuana use, effects as a "gateway" to use of other drugs, dependence on drugs, and a range of other adverse health and social consequences.

A NIDA-funded researcher at Johns Hopkins University, Baltimore, Maryland, is working with the Organization of American States Inter-American Drug Abuse Control Commission and with researchers in Costa Rica, the Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, and Panama to undertake a multisite cross-sectional school-based survey of teenage drug use in these seven countries. The project includes the use of standardized classroom survey methods and will produce estimates of drug use by teenagers in each country, based on a national probability sample. Results from the study will contribute to understanding of the characteristics of individuals, the conditions, and the processes that influence the occurrence of drug use, drug dependence, and other forms of serious drug involvement among youth.

Medications Development Division

NIDA's Medications Development Division is continuing its collaborative efforts with pharmaceutical companies to develop effective medications to treat opiate and cocaine dependence. Arrangements exist with companies in Belgium, Denmark, France, Germany, Italy, Japan, the Netherlands, Slovenia, Sweden, Switzerland, and the United Kingdom.

Through a Cooperative Research and Development Agreement (CRADA), the Division is continuing its liaison with a British pharmaceutical company to develop an application and obtain a new drug approval from the U.S. Food and Drug Administration (FDA) for the marketing of a combination product of buprenorphine hydrochloride and naloxone, to treat opiate dependence. The company is planning to file an New Drug Application (NDA) in 1999 for the buprenorphine–naloxone combination tablets. The CRADA also has resulted in the company's filing an NDA for buprenorphine mono tablets. FDA has deemed this product "approvable." The product is marketed in six countries and is under review in 17 other countries.

Activities With International and Multinational Organizations

World Health Organization

NIDA serves as a World Health Organization (WHO) Collaborating Center on Drug Dependence. The two major areas of collaboration are research and information exchange.

In 1998, the focus of the WHO-NIH (National Institutes of Health) Joint Project on Diagnosis and Classification of Mental Disorders, Alcohol- and Drug-Related Problems was concluded with completion of two diagnostic instruments: the core version 1.1 of CIDI and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Collaborative work continues on the WHO-NIH Joint Project on Disablement, a parallel project that was initiated in 1996. NIDA participated in a meeting of the instrument development task force, in Geneva, Switzerland, on March 9–12, 1998, and in subsequent deliberations of the task force. A preliminary instrument for assessment of disablement has been developed and is being field tested in a variety of cultures. Once assessment instruments are in place, pilot studies will be conducted to focus on the ability of the instruments to predict the need for and the use and cost of health care services.

As part of the WHO Multi-Centre Study of AIDS and Injecting Drug Use, NIDA researchers served as consultants to examine the relationship between (a) the self-reported behavioral change to reduce the risk of contracting AIDS and (b) the HIV serostatus of 4,419 injection drug users in 11 cities in Asia, Australia, Europe, North America, and South America. They examined this relationship by administering WHO's multisite questionnaire on risk behavior and by performing HIV testing on blood or saliva samples. Overall, the researchers found a substantial relationship between self-reported reduction in AIDS risk and actual HIV seronegative status. Despite variation across the sites, the relationship remained consistent across demographic subgroups and those with similar history of drug use. These findings indicate that injection drug users can modify behaviors that increase risk for HIV and can report accurately on behavioral changes. In addition, the researchers are monitoring trends in the seroprevalence of HIV and the incidence of immunosuppression.

Global Research Network on HIV Prevention in Drug-Using Populations

NIDA, the NIH's Office of AIDS Research, the WHO Program on Substance Abuse, and the Joint United Nations Program on HIV/AIDS were joint sponsors of the inaugural meeting of the Global Research Network on HIV Prevention in Drug-Using Populations. The meeting was held in Geneva, Switzerland, on June 25–26, 1998, just before the 1998 World AIDS Conference. This meeting was the first step toward the long-term goal of establishing a self-sustaining global communications infrastructure for rapid international communication, dissemination, and use of information on HIV/AIDS epidemiology and prevention research. Components of this infrastructure include (a) exchange and interpretation of research findings from intervention studies of drug-using populations at high risk for HIV and other blood-borne diseases; (b) translation and dissemination of research findings on prevention principles and practices that slow the rate of spread of HIV; and (c) development of new cross-national research efforts to prevent the spread of HIV and other infections among drug users.

Extramural Programs

Grants

During FY 98, NIDA supported 17 foreign grants and 14 grants with a foreign component. These grants are administered by the Division of Epidemiology and Prevention Research, the Division of Basic Research, the Division of Clinical and Services Research, and the Center on AIDS and Other Medical Consequences of Drug Abuse.

Contracts

In FY 91, NIDA created the INVEST Program. The goals of the Program are

1. to foster collaboration within the international community of scientists engaged in research on drug abuse;
2. to expand the international network of drug abuse researchers who are knowledgeable in the areas of science related to NIDA's mission;
3. to broaden the dissemination of findings from NIDA's drug abuse research to the international community; and
4. to provide scientific and technical consultation on drug abuse research to foreign investigators, ministries of health in other countries, and international organizations.

Activities supported through NIDA's INVEST Program expand international scientific knowledge about drug abuse while promoting development of rigorous scientific research. Through the Program, NIDA is building an international network of scientists capable of augmenting the research conducted and supported by the Institute.

International Meetings

During FY 98, NIDA supported several research workshops and conferences in collaboration with other countries and international organizations:

- Prevention of HIV and Other Infectious Diseases Among Drug Abusers, in St. Petersburg, Russia, in October 1997;
- U.S.-India Workshop on HIV Prevention Research Methodology, in Madras, India, in February 1998;
- U.S.-Mexico Binational Demand Reduction Conference, in El Paso, Texas, in March 1998;
- Building International Research on Drug Abuse: Global Focus on Youth, in Scottsdale, Arizona, in June 1998;
- Global HIV Prevention Research Network Inaugural Meeting, in Geneva, Switzerland, in June 1998; and
- Adolescent Drug Abuse: Assessment and Treatment, in Stockholm, Sweden, in August 1998.

Interagency Agreements

Training and Technical Assistance

Under a Letter of Agreement between NIDA and the U.S. Department of State's Bureau of International Narcotics Matters and Law Enforcement Affairs, NIDA has provided capacity-building activities in the area of drug abuse, to other countries and international organizations. Activities carried out in FY 98 include (1) training meetings on epidemiologic surveillance methods to monitor drug abuse and (2) technical assistance in development of an infrastructure to monitor drug abuse patterns and trends, to identify emerging drugs of abuse, and to specify risk factors, vulnerable populations, and health and social consequences of drug abuse. Training and technical assistance were provided in meetings in several countries.

Meetings of the East and South Asian Multi-City Epidemiology Work Groups were held in Penang, Malaysia, in November 1997 and May 1998. These work groups are composed of researchers from Bangladesh, Burma, Cambodia, China, India, Laos, Malaysia, Myanmar, Nepal, Pakistan, the Philippines, Singapore, Sri Lanka, Thailand, Turkey, Vietnam, and Taiwan.

A meeting of the South African Community Epidemiology Network on Drug Abuse was held in Cape Town, South Africa, in March 1998.

The second meeting of the U.S.-Mexico Border Epidemiology Work Group was held in Tijuana, Mexico, in August 1998.

International Epidemiology Work Group on Drug Abuse

The 5th meeting of the International Epidemiology Work Group on Drug Abuse was hosted by the European Monitoring Center on Drugs and Drug Addiction, in Lisbon, Portugal, in July 1998. The work group is a network of researchers who meet annually to present and discuss epidemiologic and ethnographic information on the current status of drug abuse in selected countries and regions of the world.

Participants included the United Nations International Drug Control Program, the WHO Program on Substance Abuse, the Organization of American States, and the Pan American Health Organization. This meeting featured reports on the status of drug use and abuse by work group members from national and regional agencies with ongoing epidemiologic surveillance programs, including

- NIDA's Community Epidemiology Work Group;
- the Canadian Community Epidemiology Network on Drug Use;
- the Inter-American Drug Abuse Control Commission's surveillance system in Central America, the Dominican Republic, and Panama;
- the European Monitoring Center on Drugs and Drug Addiction;
- the Council of Europe's Pompidou Group surveillance network in Central, Eastern, and Western Europe;
- Sistema de Vigilancia Epidemiológica de las Adicciones, Mexico;
- the South African Community Epidemiology Network on Drug Use; and
- the South and East Asian Multi-City Epidemiology Work Group.

Intramural Programs and Activities

NIDA's Intramural Research Program is located at the Addiction Research Center, Baltimore, Maryland. During FY 98, the Intramural Research Program hosted 23 Visiting Fellows, 2 supplemental Visiting Fellows, 1 Visiting Associate, 2 Visiting Scientists, 7 Guest Researchers, and 1 Special Volunteer. These visitors were from the following countries: Australia, China, Czech Republic, Germany, India, Israel, Japan, Jordan, the Philippines, Poland, Russia, Spain, and Taiwan.

Fellowships

NIDA supports two international fellowships to offer professional research development opportunities to international scientists: the INVEST Research Fellowship and the Hubert H. Humphrey Drug Abuse Research Fellowship. To support NIDA's vision for cooperation in international research, it is important to develop an international cohort of scientists who are knowledgeable about NIDA's research and are trained in accepted methods and current technology.

INVEST Research Fellowship

NIDA's INVEST Research Fellowship enables postdoctoral researchers to work with established scientists engaged in drug abuse research at a U.S. institution. Each non-U.S. scientist receives research training with a NIDA-funded grantee for 1 year. The FY 98 INVEST Research Fellows were from France, Mexico, and Russia.

Hubert H. Humphrey Drug Abuse Research Fellowship

In cooperation with the U.S. Information Agency and Johns Hopkins University, Baltimore, Maryland, NIDA sponsors a unique component of the Hubert H. Humphrey Drug Abuse Research Fellowship Program. This fellowship is designed to provide mid-career professionals in the field of drug abuse from developing countries with exposure to state-of-the-science methods and research advances. The Program also provides the basis for establishment of research linkages leading to future international research.

The Hubert H. Humphrey Drug Abuse Research Fellows funded by NIDA in FY 98 were from Hungary, India, Nigeria, and Ukraine.

XIV.

National Institute of Environmental Health Sciences

INTRODUCTION

The National Institute of Environmental Health Sciences (NIEHS) is located in Research Triangle Park, North Carolina. Since its creation in 1966, the Institute has been the primary source of Federal efforts to study how environmental factors affect human health. Because of the broad scope of the NIEHS mission, its research relies on essentially every discipline in the biological, chemical, and physical sciences.

Human health and disease result from three interactive elements: environmental factors, genetic susceptibility, and time or age. From conception to death, we are all exposed to a multitude of environmental agents with the potential to disrupt normal physiological function and cause disease. Critical to establishment and maintenance of a healthy human environment is an understanding of the biological basis of these hazards. Without such understanding, we can only guess about which human exposures should be controlled and at what levels.

The opportunity to make a difference in the environmental health sciences has never been greater. A rapid transition in the discipline, coupled with advances in genetic research, has brought scientists near to a breakthrough in the bottleneck of our lack of knowledge about the identity and mechanisms of environmental hazards that contribute to human illness. We are now poised to make enormous progress in prevention, diagnosis, and treatment of diseases associated with environmental factors. The goal is to learn which environmental or genetic components are the most important contributors to a specific disease and which individuals are most likely to develop that disease.

Environmental health problems are not perceived as local in scope or short term in nature. The most difficult issues stem from a dearth of data and understanding about the health consequences of long-term low-level exposures to environmental agents. Environmental problems have global effects on human health that may not be easily reversible or amenable to quick technological fixes. Assessing the complex environmental health problems facing today's society requires international cooperation on an unprecedented scale. NIEHS continues to take a leading role in conducting international collaborative research, training, and information exchange in environmental health.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

The International Agency for Research on Cancer (IARC) is supported by NIEHS to develop and establish a series of monographs on chemical agents that have been tested for their potential to cause human cancer. IARC is a specialized agency within the World Health Organization (WHO) that supports both biological and epidemiologic research on human cancer. Through the IARC administrative structure, specialists in the causes of human cancer are convened to develop the monographs. In each document, the literature and publicly available databases are reviewed, to assess the carcinogenic potential of a specific agent.

During 1998, several new monographs were developed. In addition, a new 5-year plan for agents to be evaluated was created. NIEHS participated in the selection of these agents, which was based on information from the National Toxicology Program, bioassay results, and findings from protocols for the screening of transgenic animals and other test systems.

The proceedings of an international workshop on Alternative Testing Methodologies, which was convened by the Scientific Group on Methodologies for the Safety Evaluation of Chemicals, was published in *Environmental Health Perspectives,* in April 1998. The workshop, attended by scientists from 16 countries, was cosponsored by NIEHS; WHO's International Program on Chemical Safety; the United Nations Environment Program; the International Labour Organization; and the Scientific Committee on Problems of the Environment, of the International Council of Scientific Unions.

The purposes of the workshop were (1) to assess methods available for use as alternatives to testing large numbers of animals to predict adverse effects of chemicals in the environment on human health and (2) to identify and recommend research to fill knowledge gaps and thus lead to development of new testing methods. Workshop topics included conceptual issues, acute toxic effects, toxic effects on organs, and ecotoxicology. A joint workshop report was prepared for each topic; the report included recommendations for the development and use of alternative testing methods. Participants concluded that there are alternative testing methods and approaches that can be incorporated into tiered strategies for toxicological assessments and that use of these methods will reduce the numbers of animals required and, in some instances, reduce animal pain and distress. It was recommended that future efforts to develop test methods should emphasize procedures that reveal mechanisms of toxic effects, to provide improved prediction of adverse health consequences. Continued international cooperation was encouraged, to facilitate future progress in the development of alternative testing methods that will contribute (a) to improved protection from environmental factors that may be harmful to human health and (b) to the safeguarding of animal welfare.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Czech Republic

An investigator in the Division of Intramural Research (DIR), Epidemiology Branch, is collaborating with the Prague Institute for Advanced Studies, the National Center for Occupational Health, Johannesburg, South Africa, and Westat, Inc., Research Triangle Park, North Carolina, to study the increased risk for lung cancer mortality in uranium workers. Risk has been clearly demonstrated for miners exposed to very high levels of radon. The investigators collected data on smoking and exposure to dust and used a population-based cancer registry to study whether there is a linkage to cancer. Vital statistics were determined for almost all of the 18,985 miners in the population. The miners had more than twice the expected incidence rate of lung cancer and increased rates for other cancers, such as leukemia and cancer of the larynx. Additional years of follow-up are planned for better assessment of some of these potential risks.

France

A researcher in the Biostatistics Branch collaborated with the Chief of the Unit of Epidemiology, IARC, Lyon, France, to analyze data on human cancer incidence. They analyzed data from the Surveillance, Epidemiology, and End Results study from 1975 through 1994, to search for unexplained patterns in cancer incidence in the United States. Their analysis focused on long-term trends in incidence and on deviations from those trends by birth cohort or time period. Unexplained increases in cancer incidence serve as indicators that may signal the emergence of new risks or the intensification of known risks. Incidence patterns can also provide clues about avoidable causes of cancer. Discovering avoidable causes is a crucial prerequisite for cancer prevention and thus remains critical for public health. Examining patterns of cancer incidence is critical in prediction of future demands for health services and in assessment of past progress against cancer. These patterns can suggest changes in underlying risk factors, and they clearly highlight the continuing need for research on the causes of this disease and on preventive measures.

Germany

An investigator from the Laboratory of Molecular Genetics is collaborating with researchers at the Pathology Institute of Ludwig-Maximilians University, Munich, the Physiology Institute II at the University of Heidelberg, and the University Neurology Clinic, Dresden, to investigate the DNA polymerase antigen in tissues that show evidence of mitochondrial dysfunction. Human mitochondrial DNA polymerase (DNA polymerase gamma) is sensitive to a wide range of antiviral nucleotide analogues, which causes inhibition of DNA synthesis. Consequently, patients being treated with antiviral therapy develop syndromes that characterize mitochondrial dysfunction. The investigator has cloned and overproduced DNA polymerase gamma in this NIEHS Laboratory.

A scientist in the Laboratory of Structural Biology is collaborating with the Faculty for Chemistry at the University of Konstanz, on the development of electrospray mass spectrometric techniques for the detection of noncovalent complexes, especially protein:DNA complexes. The scientists are investigating leucine zipper complexes and other protein–nucleotide complexes.

Italy

NIEHS biostatisticians are working with the Department of Statistical Sciences, University of Padua, in the European Study on Daily Fecundability, a large multinational study of human fertility. DIR staff have developed statistical methods to correct for measurement error in fertility studies and are applying these methods to data from the European fecundability study.

Japan

An investigator in the Laboratory of Reproductive and Developmental Toxicology collaborated with investigators in the Department of Anatomy and Developmental Biology, Graduate School of Medicine, Kyoto University. The investigators are isolating and characterizing spermatogenic cell-specific mRNAs of mouse and human type 1 hexokinase (HK1); cloning and characterizing the mouse Hk1 gene; studying the synthesis of HK1 protein in spermatozoa; and determining the role of HK1 protein in energy production of spermatozoa. Other joint research projects include analysis of the phenotype of mice with targeted mutations in the Hsp70-2 gene; identification of the stage of germ cell development when meiotic arrest and apoptosis occur in Hsp70-2 knockout mice; and analysis of the occasional escape from meiotic arrest of germ cells in Hsp70-2 gene knockout mice. The investigator is also working with investigators from the Laboratory of Molecular Pathology, Department of Immunology, National Institute of Animal Health, Tsukuba. The research team is analyzing the regulation of expression of the Hsp70-2 gene, by using transgenic mice and in vitro procedures to identify binding sites for transcription factors. Related research includes identification of transcription factors involved in expression of the Hsp70-2 gene, by cell type and developmental stage; identification and characterization of proteins that bind to meiotic "hot spots" in recombinant DNA; localization of and determination of the function of hot-spot binding proteins during spermatogenesis; and study of the association of the p53 gene, polyadenosine diphosphate polymerase, and DNA topoisomerase II with hot spots.

A scientist in the Laboratory of Computational Biology and Risk Analysis is collaborating with scientists at the National Institute for Environmental Studies, Japan, on the direct effect of global warming on human morbidity. Because of the greenhouse effect, surface temperatures could rise by 1–3° C. A greater frequency and duration of heat waves could accompany an increase in surface temperature, especially during the warm summer months. As a result, there could be a greater incidence of heat-related morbidity and mortality, especially in large cities.

Mexico

A researcher in the Laboratory of Pulmonary Pathobiology collaborated with researchers in the Division of Basic Investigation, National Cancer Institute of Mexico, and the University of Mexico, Mexico City, on cellular and molecular mechanisms of particulate-induced lung disease. There is a growing interest by Mexican scientists in the major problems related to the frequently heavy air pollution of Mexico City. Joint research focuses on the basic cellular and molecular mechanisms by which air pollution particles in Mexico City cause lung conditions such as asthma and airway inflammation.

Middle East

A member of the Toxicology Operations Branch is the NIEHS coordinator for the Middle East Pesticides Program sponsored by the U.S. Agency for International Development. This program involves scientists from nine Middle East countries and areas: Bahrain, Egypt, Israel, Jordan, Kuwait, Lebanon, Saudi Arabia, the United Arab Emirates and Yemen, and Gaza and the West Bank. These scientists are working with scientists from Canada and the United States to address and assess environmental health risks in the Middle East region. The group is studying ways to reduce the adverse health effects of pesticide use, while promoting regional cooperation among environmental health scientists.

The Netherlands

A scientist in the Laboratory of Experimental Pathology continues to collaborate with scientists at the Laboratory of Health Effects Research, National Institute of Public Health and Environment, the Netherlands. This work, entitled Phenolic Phytoprotectants—Role in Preventing Initiation, Promotion, and Progression of Cancer, is testing whether the specific phytoprotectant TgNK (MMTV/c-*neu*) can delay or prevent mammary cancer.

An investigator from the Laboratory of Signal Transduction collaborated with colleagues at the Research Institute of Toxicology, Utrecht University, the Netherlands, on the Promiscuous Coassembly of Serotonin 5-HT3 and Nicotinic Alpha 4 Receptor Subunits Into Ca^{2+}-Permeable Ion Channels. Serotonin 5-hydroxytryptamine type 3 receptors (5-HT3R) and nicotinic acetylcholine receptors are structurally and functionally related proteins, yet distinct members of the family of ligand-gated ion channels. The receptors for most members of this family are diverse heteromeric receptors. In contrast, the known 5-HT3R subunits are homologues of the same 5-HT3R-A subunit, but they form homopentameric receptors. The investigators have shown, by heterologous expression followed by immunoprecipitation, that 5-HTR and nicotinic acetylcholine receptor alpha 4 subunits coassemble into a novel type of heteromeric ligand-gated ion channel, which is activated by 5-HT.

United Kingdom

In joint work with the Imperial College, London, England, the Laboratory of Molecular Genetics is exploring the role of the nuclear DNA primase complex responsible for priming DNA replication. Using x-ray diffraction, the investigators plan to study the three-dimensional structure of the two primase subunits.

Taiwan

A member of the DIR Epidemiology Branch was a visiting Professor of Public Health at the National Cheng Kung University Medical College, Tainan, Taiwan, during May 1–August 1, 1998. The scientist worked on follow-up of the Yucheng cohort that was exposed to PCBs (polychlorinated biphenyls) and PCDFs (polychlorinated dibenzofurans) in 1979.

Activities With International and Multinational Organizations

European Commission and European Union

The European Commission and the European Union are developing a 5-year plan for cooperative international research in a number of areas dealing with sustainable development. Disruption of endocrine processes was selected as an area for trans-Atlantic research partnerships that would be sponsored through funding at European institutions. In cooperation with the U.S. Environmental Protection Agency (EPA), NIEHS had a leading role in planning this research at a workshop at the National Academy of Sciences, in Washington, D.C., in the spring of 1998.

International Agency for Research on Cancer

The Toxicology Operations Branch of the National Toxicology Program (NTP) provides information to IARC for the Directory of Agents Being Tested for Carcinogenicity. NTP submits updates for the IARC directory approximately every other year. The NTP survey was started in 1973 to collect information on planned and ongoing long-term carcinogenicity testing, from organizations throughout the world. The purposes of the survey are to avoid unnecessary duplication of research, to increase communication among scientists, and to update information on research facilities and the chemical agents being tested. The NTP updates include a list of planned long-term and exploratory dose-finding studies, a status report on ongoing studies, and a current list of completed studies. This information was submitted to IARC in May 1998.

Two investigators in the DIR Toxicology Operations Branch traveled to Lyon, France, to assist IARC's efforts to put abstracts from the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* on the IARC Web site. Files of monograph abstracts were electronically transferred to IARC.

An investigator in the Toxicology Operations Branch participated in a meeting for preparation of volume 71 of the IARC monograph series. The meeting, which was convened to discuss reevaluation of certain industrial chemicals, was held in Lyon, France, on February 17–24, 1998.

International Arctic Monitoring and Assessment Program

NIEHS plays a leading role in the International Arctic Monitoring and Assessment Program, which is an attempt to define environmental health problems of arctic populations. Pollutants such as heavy metals (e.g., mercury) and persistent organic substances (e.g., chlorinated pesticides) move through the environment, and they tend to be deposited in colder climates. In addition, native populations eating foods from the top of the food chain tend to ingest more of these pollutants. The goal is to determine the severity of the problem and recommend public health countermeasures as needed. Through several joint activities, NIEHS is participating in the design of research programs to answer these questions. One activity under way is a workshop on the use of biomarkers to facilitate epidemiologic studies of cause–effect relationships between environmental exposures and effects on health. This workshop involves scientists and public health officials from all the arctic countries and the U.S. agencies involved in arctic research—the National Institutes of Health, the National Science Foundation, the National Oceanic and Atmospheric Administration, the National Aeronautics and Space Administration, and EPA.

International Collaborative Project on Micronucleus Frequency in Human Populations

A scientist in the Laboratory of Pharmacology and Chemistry was a member of the coordinating committee of the International Collaborative Project on Micronucleus Frequency in Human Populations. The other members of the committee are from the Department of Human Nutrition, Adelaide, Australia; the Department of Environmental Epidemiology, Istituto Nazionale della Ricerca sul Cancro, Genoa, Italy; the School of Public Health, University of California, Berkeley; and the Institute of Public Health, National Yang Ming University Medical School, Taipei, Taiwan. This project was organized to collect data on background micronucleus frequencies in lymphocytes and exfoliated cells from different human populations. The information will be used to determine the extent of variation of baseline micronucleus frequencies for different laboratories and the influence of other factors potentially affecting these values; to examine the effect of protocol variations on measurement of micronucleus frequency; to design optimal test protocols; and to determine the extent to which micronucleus frequency is a valid biomarker of aging and risk for diseases such as cancer.

International Program on Chemical Safety

Through the WHO International Program on Chemical Safety (IPCS) and the European Union, NIEHS is providing leadership to establish an international scientific strategy to assess effects on human health from exposure to environmental estrogens. There are many questions about the effects of synthetic and natural estrogens on human reproductive capacity and disease. Investigators at several international scientific organizations and regulatory agencies are developing procedures for screening and testing chemicals for the ability to disrupt normal endocrine processes and are determining baseline data for these tests. NIEHS has some of the world's experts on disruption of endocrine processes, and they participate heavily in both the political and scientific discussions of appropriate strategies for understanding and managing the hazards of these environmental chemicals.

NIEHS staff participated in several oversight committees of the WHO IPCS, giving guidance for future directions and initiatives in research. With a change in executive leadership in WHO and with its subsequent reorganization, NIEHS and other U.S. agencies are advising that IPCS elaborate its role in world health by focusing on protection of persons who live and work in the most polluted environments. Control of hazardous environmental agents is as important as control of infectious diseases, and the consequences of failure to control these agents can be as dire as failure to control infectious agents, even though manifestations of disease can be more protracted.

A member of the Laboratory of Toxicology served as corapporteur for the IPCS Task Group that is composing the environmental health criteria, Scientific Principles and Methods for Addressing Allergic Hypersensitization Associated With Exposure to Chemicals. She also serves on the Expert Review Panel for the Ad Hoc Working Group on Immunotoxicity, of the Organization for Economic Cooperation and Development (OECD). This committee recently evaluated and recommended revisions to OECD test guideline 407 (28-Day Oral Toxicity Studies in Rodents) and will develop criteria for the classification of substances that are hazardous to the immune system. In addition, the scientist was a reviewer for the Criteria for Classification of Skin- and Airway-Sensitizing Substances in the Workplace and General Environment. She was a member of the organizing committee for an international symposium, entitled Advancement of Epidemiological Studies in Assessing the Human Health Effects of Immunotoxic Agents in the Environment and the Workplace, which was held at the National Institute of Public Health and the Environment, in Bilthoven, the Netherlands, in the spring of 1998. The meeting gathered experts in epidemiology, clinical immunology, and immunotoxicology, to formulate a consensus on the most useful approaches for assessment of immunotoxic effects in humans. The meeting was cosponsored by the National Institute of Public Health and the Environment, the Netherlands; IPCS; the World Resources Institute; the European Union; the European Science Foundation; the Centers for Disease Control and Prevention; the National Institute for Occupational Safety and Health; NIEHS; EPA; and the American Crop Protection Association.

With NIEHS support, IPCS announced the start of work on a state-of-the-science document on assessment of chemicals that may disrupt endocrine processes. The IPCS document will further detail the research needed in specific areas and will better define possible hazards from the many chemicals in the environment that can mimic the actions of hormones.

Extramural Programs

A large portion of the NIEHS financial resources supports extramural programs, including grants, cooperative agreements, and contracts that are awarded competitively to academic and research institutions. The Extramural Division offers a broad range of research opportunities for foreign scientists. In 1998, 30 research projects were undertaken in Argentina, Australia, Canada, Chile, China, Denmark, Faroe Islands, France, the Gambia, Italy, Japan, Mexico, Norway, Seychelles, Singapore, South Korea, Switzerland, Yugoslavia, and Taiwan.

Research Grants

In fiscal year 1998, NIEHS provided the following grant support:

- to IARC for travel and subsistence of non–U.S. government participants in international conferences and for preparation, printing, and distribution of IARC publications;
- to WHO for support of IPCS;
- for an epidemiologic study in collaboration with Argentinean investigators at several sites, to examine the relationship between bladder cancer and arsenic exposure in Argentinean populations;
- for investigation of the relative contribution to the infant in utero of the mother's current environmental exposure to lead, compared with mobilization of lead from maternal stores, especially from bones, in Adelaide, Australia;
- for a study at the University of Victoria, British Columbia, focusing on the potential contribution of electromagnetic fields to mutagenesis, in conjunction with free-radical–producing mutagens, in a cell line of fibroblasts from transgenic rats;
- to researchers at Toronto Hospital, Ontario, for study of the hypotheses (a) that PCBs adversely affect development of both the male and female reproductive and cen-

tral nervous systems, via at least three mechanisms independent of the cellular receptors by which they are thought to operate, and (b) that these adverse effects occur at concentrations of PCBs that are relevant to occupational exposure if not to environmental exposure;

- for a continuing study of the relationship between exposure to PCBs and thyroid function and development of the central nervous system in infants of the native Inuit population in Canada and for extension of this study, by Danish investigators, to a cohort of Greenland Inuit;
- for study of the relationship between airborne acidic air pollutants and the respiratory health of approximately 3,300 children in late adolescence who are living in 15 communities in Canada and the United States;
- for dissemination of training and evaluation materials for institution of a train-the-trainer program, where feasible, and for training of firefighters when no qualified instructors are available, in Canada and the United States;
- for research to validate a challenge test for arsenic in persons exposed to DMPS (2,3-dimercapto-1-propanesulfonic acid) in populations in Northern Chile and Mexico;
- for a molecular biology–epidemiologic study to identify specific chromosome alterations in workers exposed to benzene in China;
- for research (a) to develop and validate molecular biomarkers of exposure to aflatoxin in carriers and noncarriers of hepatitis B virus, in Qidong Province, China, and the Gambia; (b) for follow-up of a prospective cohort in rural China to examine the relationships and interaction among levels of aflatoxin biomarkers, intrinsic risk factors, and disease outcome; and (c) to determine the effect of primary prevention methods in Guinea, West Africa, by using a targeted strategy to reduce contamination in community settings, as evidenced by lower levels of aflatoxin biomarkers;
- for a study in China to determine whether biomarkers of aflatoxicosis caused by consumption of aflatoxin-contaminated foods can be modulated by ingestion of oltipraz or chlorophyllin;
- for research to compare reproductive function in two populations in China—one in a highly industrial area with multiple sources of exposure to industrial lead and one in a rural area with few opportunities for exposure to lead;
- for evaluation of a common polymorphism at the gene locus for aminolevulinate dehydrase, which is associated with elevated lead levels in blood of children and adults, to determine whether the polymorphism is a useful biomarker for effectiveness of a chelation therapy used in the treatment of lead poisoning in a population in Anhui Province, China;
- for development of a significantly more sensitive and rapid method of identifying benzene exposure, a method that has been applied to human blood samples obtained from workers exposed to benzene in China;
- for research to refine and validate molecular biomarkers of human exposure to aromatic and heterocyclic amines and to use the biomarkers to determine the role of heterocyclic amines in the risk of colon cancer and the role of aromatic amines in the risk of bladder cancer in smokers and nonsmokers in defined cohorts in China, Japan, and Singapore;
- for a study to determine whether patients with breast cancer in Denmark had an increased body burden of organochlorine compounds, as reflected in the serum concentration before the disease developed;
- for studies to assess the neurobehavioral effects of prenatal exposure to PCBs on the developmental outcomes for the offspring on the Faroe Islands;
- for an epidemiologic study of workers in France who have been exposed to vinyl chloride in the manufacture of polyvinyl chloride (a) to investigate the possibility of differential genetic susceptibility, by using mutation frequencies in biomarkers in blood lymphocytes, (b) to examine DNA repair capability, and (c) to evaluate whether the presence of a mutated protein is a predictor of high frequencies of mutation, a predictor of high risk for developing liver angiosarcoma, and an early marker of the onset of liver angiosarcoma;
- for an epidemiologic study of the risk of endometriosis in women who were exposed to high levels of dioxins after a chemical company explosion in Seveso, Italy;
- for a prospective study of (a) the importance of lead in bone matrix and of DMSA-chelatable lead in soft tissue and (b) the effect of modification by the aminolevulinate dehydrase genotype, in the prediction of important health outcomes in a population of battery makers exposed to lead, in Korea;
- for a project in Mexico City, Mexico, to examine the effect that maternal bone stores of lead accumulated from environmental exposures have on fetuses and infants during pregnancy and lactation;
- for outreach to jointly sponsor conferences with Mexican colleagues that address problems related to hazardous wastes and their dump sites;
- for a population-based case–control study on the role of heredity and environment in the occurrence of cleft lip and palate, in Norway;
- for research to examine the neurodevelopmental effects of long-term exposure to low levels of methyl mercury (MeHg) in cohorts of children living in Seychelles, who are exposed to the compound by eating fish;
- for an epidemiologic study in a smelter town and in an unexposed town in Yugoslavia (a) to determine whether the adverse effects of lead exposure persist beyond early childhood and (b) to test the hypothesis that there may be a strong association between cognitive function and concentration of lead in bones—the best marker of cumulative lead exposure;
- for a molecular biology–epidemiologic study in Taiwan, to assess the relationship between exposure to aflatoxin, as quantified by aflatoxin B_1–DNA adducts, hepatitis B status, and liver cancer; and
- for a population-based case–control study of squamous cell carcinoma of the skin and of bladder cancer in an area of Taiwan where exposure to arsenic through drinking water is still substantial.

International Training and Research in Environmental and Occupational Health Program

NIEHS continues to participate with the Fogarty International Center, the National Institute for Occupational Safety and Health, and the Centers for Disease Control and Prevention in supporting the International Training and Research in Environmental and Occupational Health Program, a grant program for foreign scientists that is aimed at developing international training and research programs related to environmental health. A major goal of the program is to train scientists of other countries to deal effectively with environmental and occupational health problems through epidemiologic research, environmental monitoring, engineering control, and communication.

Through this program, awards are made to U.S. investigators to support the training of foreign nationals. The program provides for training at U.S. universities and institutions and for in-country training and is followed with financial assistance for conducting research in the trainee's home country. Participants in this program are foreign nationals who are involved in environmental or occupational health research and prevention activities in their home countries.

The training program extends to scientists and institutions in Central and South America, Eastern Europe, Thailand, Ukraine, and Vietnam.

International Meetings

During fiscal year 1998, NIEHS was involved in various capacities in international meetings. The Institute hosted an international meeting of the OECD Steering Committee on In Vitro Percutaneous Absorption Test Methods, in Paris, France, in October 1997. The committee developed a plan to objectively evaluate proposed in vitro test methods for assaying the percutaneous absorption of chemicals, with the goal of eventual adoption of internationally harmonized test guidelines that can be used by the 29 member countries of OECD.

In addition, NIEHS was a lead agency and an invited participant at a European Centre for the Validation of Alternative Methods Workshop on Strategies for Validation and Acceptance of Alternative Toxicological Methods, convened in Zürich, Switzerland, in January 1998. The workshop was sponsored by the center and the European Research Group on Alternatives in Toxicological Testing. Participants at this meeting developed recommendations for international harmonization of validation and regulatory acceptance processes, which would facilitate international adoption and use of new improved testing methods.

The NIEHS Laboratory of Signal Transduction organized an international symposium on Nuclear Receptors and Transduction, which was held in Keystone, Colorado, in April 1998.

NIEHS also provided partial support for a conference entitled Women's Health: Occupation, Cancer, and Reproduction, in Reykjavik, Iceland, on May 14–16, 1998.

In June 1998, NIEHS cosponsored the general assembly of the Scientific Committee on Problems of the Environment, of the International Council of Scientific Unions. The assembly was held at the Robert Wood Johnson Medical School, New Jersey. The scientific committee was established in 1969 to provide interdisciplinary input on international scientific problems involving the environment. Thirty-nine countries participate in this effort. The theme of the 1998 assembly was Towards Sustainability, and speakers addressed scientific, legislative, and cultural aspects of global, regional, and local environmental issues.

NIEHS supported a session on the effects of radiation exposures on health, at the joint meeting of the International Society for Environmental Epidemiology and the International Society for Exposure Assessment, in Boston, Massachusetts, in August 1998. Support for this session was part of a larger effort by NIEHS to stimulate research on methods to better assess levels of exposure to environmental agents. One goal of this effort is more powerful epidemiologic studies.

NIEHS scientists participated in an OECD Workshop on the Validation of Endocrine Disrupter Screening and Testing Methods, in Washington, D.C., on August 10–11, 1998. The objective of this meeting of expert consultants was to define which test methods should undergo validation and how this work should be organized. U.S. government agencies are working closely with OECD to ensure that test methods selected for international validation will also be useful as part of the EPA Endocrine Disrupter Screening and Testing Panel, which is being validated and implemented in response to recent U.S. legislation. The U.S. Interagency Coordinating Committee on the Validation of Alternative Methods, supported by the NTP Center for the Evaluation of Alternative Toxicological Methods, has been invited to participate in the OECD management committee that will provide oversight of the upcoming international validation studies.

NIEHS provided partial support for the 3rd International Symposium on Hormonal Carcinogenesis, at the University of Washington, Seattle, in September 1998.

In addition, the Institute provided support for international attendees at the fall meeting of the Society for Occupational and Environmental Health, in Bethesda, Maryland, and the WHO Office of Global and Integrated Environmental Health.

NIEHS also funded some publication costs for workshop proceedings for the U.S.-Mexico Border Conference on Women's Health.

Intramural Programs and Activities

The Director of the Laboratory of Molecular Carcinogenesis has an agreement with English and German researchers to analyze KAI1 gene expression in lymphatic tumors and pancreatic cancer, respectively. The Director is also collaborating with IARC, Lyon, France, in examination of the possible tumor-suppressor gene Hic5 in squamous cell carcinomas; with Nippon Dental University, Tokyo, Japan, on a long-term study to examine potential carcinogens and carcinogenic mechanisms in in vitro cell systems; and with Tottori University, Yonago, Japan, in the cloning of novel telomerase suppressor and senescence genes. In addition, collaboration with Switzerland has recently been established, to study the effect of somatostatin analogues on the development of prostate tumors.

A researcher from the Laboratory of Pharmacology and Chemistry is working with researchers in Germany and Switzerland, to elucidate the mechanisms of xenobiotic transport in renal proximal tubule and in brain capillary endothelium. He is also studying hormonal regulation of renal xenobiotic transport with scientists at the University of Nijmegen, the Netherlands. This work was highlighted at an international meeting on The Cellular and Molecular Biology of Xenobiotic Transport, at NIEHS, in Bethesda, Maryland, in August 1998.

A scientist in the Biostatistics Branch is collaborating with a scientist at the National Center of Hygiene, Ecology, and Nutrition, Sofia, Bulgaria, to measure the variability of lipid peroxides over time, in pregnant and nonpregnant women. She is also working with Health Canada, Ottawa, Ontario, in a study to correlate PCBs, dioxins, and furans in human tissues with lipid peroxidation. With scientists at the Forschungsgesellschaft mbH, Hamburg, Germany, and the Institute of Pediatrics, Obstetrics, and Gynecology, Kiev, Ukraine, the scientist is engaged in a study to determine the degree of environmental contamination (organochlorines, metals, and polycyclic aromatic hydrocarbons) in biological samples (breast milk and placenta) and to observe the reproductive outcomes in a group of women from Ukraine. Joint research with the National Cheng Kung University Medical College, Tainan, Taiwan, is focusing on gender ratios in babies born to women in the Yucheng cohort, who were exposed to PCBs and furans in 1979.

An investigator from the Laboratory of Computational Biology and Risk Analysis is collaborating with colleagues at the Department of Pharmaceutical Sciences and Biotechnology Center, University of Ferrara, Italy, on design and synthesis of opioid peptide agonists and antagonists and on bioassays of opioidmimetics. He is also studying the design and synthesis of opioid peptides and nonpeptide compounds with the Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Japan.

A researcher in the Epidemiology Branch is working with the Instituto Nacional de Salud Publica, Cuernavaca and Morelos, Mexico, on two studies: (1) a pilot study to assess exposure to PCBs in Mexico City and (2) a study of health effects of exposure to DDT (dichlorodiphenyltrichloroethane) in southern Mexico, where DDT is still used to control mosquitoes. In addition, he is collaborating with workers at the Center for Toxicology of Quebec, who will be analyzing serum specimens for DDT metabolites for the Mexican study. The researcher also has collaborated with Spanish researchers on two studies: (1) Determinants of DDT Metabolite Concentration in Adipose Tissue in Women From Five European Cities and (2) Serum β-Carotene and Colorectal Cancer: Pooled Data From Four Cohorts and a Meta-analysis.

XV.
National Eye Institute

INTRODUCTION

The mission of the National Eye Institute (NEI) is to reduce the prevalence of blindness, visual impairment, and eye disease worldwide through basic and applied research and training. Although excellent ophthalmic procedures and systems for delivery of eye care are generally accessible in the developed world, adequate health care is not readily available in all parts of the developing world. This widening gap in visual health between developed and developing nations threatens to have ominous consequences. If present trends continue, the number of blind people—estimated at 24 million worldwide—will more than quadruple during the next 40 years. As many as 90% of these blind people will live in developing countries.

Such large-scale disablement caused by blindness is not only a costly obstacle to economic development; it is also a catastrophic loss of human potential in the areas of the world most desperately in need of a healthy workforce. In addition, more than 80% of all cases of blindness can be considered avoidable; they could have been prevented or could be cured with use of technology that is available and appropriate to the resources of the community. Such deprivation is a needless denial of a basic human right for millions of people. Therefore, NEI undertakes international activities to facilitate the development and application of effective prevention and treatment programs. These efforts are coordinated by the Institute's Office of International Program Activities, which was created in February 1989. This Office enhances NEI's international programs by

- evaluating available health care technologies, promoting the most cost-effective prevention and treatment programs, and encouraging their availability for affected populations, especially in developing countries;
- conducting collaborative applied research studies to develop preventive methods for specific eye diseases;
- performing controlled clinical evaluations of promising research findings; and
- exchanging information on recent scientific advances and their appropriate application to vision problems.

NEI supports international research on six blinding diseases that have a major worldwide impact: cataract, onchocerciasis, ocular toxoplasmosis, glaucoma, diabetic retinopathy, and vitamin A deficiency.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Scientists in NEI's Ophthalmic Clinical Genetics Section, Clinical Branch, have continued their collaboration with scientists in hospitals, clinics, and medical schools outside the United States, in successful efforts to map genes for some inherited diseases. In joint efforts with scientists at the L. V. Prasad Eye Institute, Hyderabad, and the Sankara Nethralaya Hospital, Madras, India, and the Akdeniz University, Antalya, Turkey, NEI investigators continue to make important headway in efforts to map autosomal-dominant and autosomal-recessive genes for cataract.

Scientists from the Section are also working with investigators from the L. V. Prasad Eye Institute on productive mapping studies of autosomal-recessive genes for retinitis pigmentosa and gelatinous corneal dystrophy. In addition, studies of Bietti crystallin dystrophy and gelatinous corneal dystrophy are being carried out jointly with Juntendo University, Tokyo, Japan, and National Taiwan University Hospital, Taipei.

These successful collaborations, which have grown over the past several years, have also involved the training of scientists from foreign institutions in modern techniques for study of molecular genetics. These scientists are often trained by spending about 1 year in the laboratories of the Ophthalmic Clinical Genetics Section.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Barbados

The Barbados Eye Study is a series of epidemiologic investigations conducted among the adult population of Barbados (ages 40–84 years). These studies focus on measurement of the frequency of open-angle glaucoma and assessment of the occurrence of cataract, age-related macular degeneration, and diabetic retinopathy, as well as the factors responsible for these conditions.

These studies began in 1988 with examination of 4,631 individuals for visual acuity, visual field, intraocular pressure, blood pressure, and the presence or absence of diabetes. Four years later in 1992, 3,400 of the 4,631 individuals were reexamined to determine whether existing eye disease had progressed and whether new eye disease was present. The Barbados Incidence Study of Eye Disease II is continuing follow-up of the surviving cohort for comparison with baseline data. Over a 9-year period, the study will obtain data on incidence, progression, and risk factors for open-angle glaucoma, cataract, and visual impairment.

Belgium

Scientists from NEI's Laboratory of Mechanisms of Ocular Diseases are collaborating on studies of the relationship of changes in retinal blood vessels to other changes in protein-deficient rats—low blood levels of taurine, high levels of cerulean, decreased numbers of blood vessels in the brain, and enlarged liver. This work is being performed with scientists at the Catholic University of Louvain, Brussels.

In addition, scientists from this NEI Laboratory and the Catholic University of Louvain are investigating the effects of severe protein deficiency on retinal structure. They are studying damage to retinal blood vessels and its possible relationship to the angiogenesis of diabetic retinopathy.

Brazil

NEI has cooperated with the National Institute of Allergy and Infectious Diseases, National Institutes of Health, and with Escola Paulista de Medicina, Clinica Erexim, and Laboratory Fleury, São Paulo, to develop a research program on the immunology, basic mechanisms, and epidemiology of toxoplasmosis in southern Brazil. The prevalence of ocular toxoplasmosis in this population was more than 30 times higher than previous estimates for the same condition elsewhere in Brazil. In this population, ocular toxoplasmosis appears to be a sequela of postnatal rather than congenital infection. Studies performed in 1993 on blood from newborns in southern Brazil showed a low percentage of newborns with immunoglobulin M positivity, further suggesting that the disease in southern Brazil is acquired. A second survey was conducted in another part of the country. The survey shows an extremely high prevalence of toxoplasmosis, indicating that this disease is not isolated in a particular region of Brazil. Such information will be very useful in the effort to develop a comprehensive treatment program.

China

NEI is working with Peking Union Medical College Hospital in conducting a survey of the prevalence of blindness and outcomes of cataract in Shunyi County, outside Beijing, and with the Zhongshan Ophthalmic Center in conducting a survey in Doumen County. These projects are similar in design and scope to a project carried out in Nepal. The World Health Organization (WHO) and the Lions Clubs International Foundation are collaborating in sponsoring this work, which has led to publication of several research papers.

Czech Republic

Scientists from NEI's Laboratory of Molecular and Developmental Biology are collaborating with an investigator at the Laboratory of Transcriptional Regulation, Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, on cloning the crystallin cDNAs (complementary DNAs) and Pax transcription factors of the scallop. In both scallops and mammals, including humans, the lens crystallin is an aldehyde dehydrogenase. Thus, development of the scallop eye is especially relevant to development of the mammalian eye and even the human cornea.

France

Scientists in the Laboratory of Sensorimotor Research, together with a former colleague who is now at Centre de Recherches en Neurosciences Cognitives, Marseille, are studying a newly discovered optical illusion in which stationary rotating objects in the peripheral visual field are mistakenly perceived to be moving.

Germany

Scientists from NEI's Laboratory of Molecular and Developmental Biology are working with an investigator at the Institute of Mammalian Genetics, GSF National Research Center for Environment and Health, Neuherberg, to explore the molecular basis for genetic cataracts in two strains of mice (Cat2nop and Cat2t). The Cat2nop mouse carries a mutation in the gene for gamma b crystallin, and the Cat2t mouse carries a mutation in the gene for gamma e crystallin. Both mutations result in a truncated gamma crystallin protein that produces a nuclear cataract. A graduate student from the Institute of Mammalian Genetics, working in the NEI Laboratory, has found that the Cat2nop cataract may be caused by apoptotic events, whereas the Cat2t cataract is due to early arrested growth of primary fiber cells, with secondary apoptotic events.

Other scientists from this NEI Laboratory are collaborating with investigators at the University of Pennsylvania, as well as the GSF National Research Center for Environment and Health. These scientists are characterizing, at the molecular level, a genetic cataract generated by gamma irradiation. They have found that the mutation is localized to a gene that encodes for the major intrinsic protein of the ocular lens fiber membrane. A research paper on the identification and characterization of a loss-of-function mutation in the MIP gene, which results in autosomal-dominant cataract in Hfi mice, has been submitted for publication.

In addition, scientists from the Laboratory of Molecular and Developmental Biology are working with an investigator at the University Erlangen-Nürnberg, in Erlangen, to complete experiments on (a) the effects of transforming growth factor β (TGF-β) on differentiation of the cornea and (b) production of transgenic mice having the ability to activate another transgene whenever they are given tetracycline. This research will lead to the ability to turn on a foreign gene in transgenic mice.

India

Under the 1983 Indo-U.S. Science and Technology Initiative, NEI and the Indian Council of Medical Research have developed a joint research program that includes projects to reduce blindness due to cataract in India. Government of India funds for the work come through the Indian Council of Medical Research, and U.S. Government funds are provided through NEI and the National Science Foundation. In addition, NEI collaborates with Indian scientists under the U.S.-Indo Subcommission program.

The NEI Director and the Associate Director for Applications of Vision Research have continued to participate as consultants to the World Bank in developing, with the government of India, the Indian National Blindness Control Project. They have provided technical assistance in the establishment and review of training programs and have developed criteria and guidelines for cataract surgery, thus enabling a twofold increase in cataract extractions, with explicit attention to the quality and extent of restoration of vision.

The Director and Associate Director have continued to work during fiscal year 1998 (FY 98) with physician-scientists at the Dr. Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi. They have initiated a joint research project to develop and evaluate a questionnaire on vision function and quality of life that would be suitable for administration across subpopulations within India. The plan is to follow a research process similar to that used in the United States for development of NEI's Visual Functioning Questionnaire, including the use of patient focus groups to collect information on the variety and extent of day-to-day vision-related problems faced by visually impaired individuals.

Intramural scientists from NEI's Laboratory of Mechanisms of Ocular Diseases have collaborated with colleagues at the Centre for Cellular and Molecular Biology, Hyderabad, to study aging-related modifications to lens crystallins. Cataract typically occurs at an earlier age and is more heavily pigmented in subjects in India than in those in the United States. To elucidate the molecular mechanisms underlying this difference in color, the scientists are comparing the fluorescence spectra for healthy, intact lenses from subjects in India over a wide range of ages with the spectra for eye-bank lenses from age-matched subjects in the United States. The lenses from Indian subjects have substantially greater amounts of pigmented fluorescent compounds than those from U.S. subjects. These compounds, through their ability to function as photosensitizers, may contribute directly to cataractogenesis.

Another joint effort is the study of the proteins in cataract in Indians. In an attempt to elucidate processes that may contribute to the early onset and high incidence of cataract in India, researchers are comparing the crystallin properties of cataractous lenses from Indians with those of healthy or cataractous lenses from eyes of age-matched, eye-bank donors in the United States. The different forms of crystallins that have been identified are being further characterized to determine the mechanisms involved in the expression and formation of these proteins.

In addition, molecular geneticists at NEI have initiated gene-linkage studies with scientists at Osmania University and the L. V. Prasad Eye Institute, Hyderabad. Participants in these studies are members of selected families with hereditary cataract. The prevalence of consanguineous marriages in this region of India greatly increases the likelihood of recessive cataract phenotypes. A geneticist from Osmania University, who was trained at NEI in relevant techniques, has returned to Hyderabad to establish a laboratory, so that gene-linkage analysis in individuals with suitable pedigrees can be performed in India. In one family, the cataract trait has been linked to a particular chromosome, and a potential candidate gene has been identified.

An NEI-supported, randomized clinical trial at the Aravind Eye Hospital, Madurai, has been completed. In this study, treatment using intracapsular cataract surgery plus eyeglasses for the resulting aphakia was compared with treatment using extracapsular cataract extraction plus implantation of an intraocular lens. The trial's primary purpose was to compare complications during the operation and postoperative complications by 1 year after the operation. Secondary evaluation end points included (a) measurement of vision function assessed by interview, with use of a multi-item questionnaire, and (b) appraisal of economic impact on direct and indirect costs associated with blindness and cataract surgery. A randomly selected subgroup will have a 4-year follow-up to investigate the prevalence of opacification of the posterior capsule.

Israel

Studies on the relationship of the altered metabolism of special strains of the desert rat to diabetic cataract and retinopathy in these rats are being conducted with investigators at the Hadassah Medical Organization, Jerusalem.

Investigators in NEI's Laboratory of Mechanisms of Ocular Diseases are collaborating with scientists in Jerusalem to investigate the relationships of the diabetes-induced retinal microaneurysms and other angiopathies of water-thrifty desert rats with those found in other animal models of diabetic retinopathy. They are also studying corneal alterations in a rabbit model of congenital glaucoma with scientists in Tel Aviv.

Studies are being conducted with scientists at the Hebrew University-Hadassah Medical School, Jerusalem, on digitalis-like compounds in the lens of the eye. These compounds, which are present in human lenses, interfere with the basic mechanism of osmoregulation in cells. The compounds have been found in cataractous lenses, and it is possible that they are involved in lens opacification. These studies are designed to determine the location of such compounds in the lens and whether they increase with age.

Italy

Scientists in NEI's Laboratory of Mechanisms of Ocular Diseases are working with investigators from the University of Modena and the University of Pisa in studying the role of oxidative stress in age-related cataract. The approach has been to use aldose reductase, an enzyme that has an important role in diabetic cataract, as a model enzyme to study the effects of oxidation on structure and function. In addition, the scientists are investigating the mechanisms involved in modifications of crystallin that occur during development of the fiber cells of the lens.

The Collaborative Italian-American Clinical Trial is being conducted to evaluate the effect of multivitamin supplements on the risk of cataract development and progression. To date, 1,020 subjects have been randomly assigned to receive either a multivitamin and mineral supplement or a placebo; subjects will be monitored for 5 years. The study's principal investigators are at the University of Parma and NEI. The Laboratory for Epidemiology and Biostatistics, Istituto Superiore di Sanità, Rome, and the Division of Biometry and Epidemiology, NEI, serve as the study's coordinating centers. About 77% of the study cohort has had 1 year of follow-up, and 33% have been monitored for 2 years.

Japan

Scientists in NEI's Laboratory of Mechanisms of Ocular Diseases are collaborating in studies of the effectiveness of aldose reductase inhibitors in preventing a corneal epitheliopathy in rats that is similar to the epitheliopathy resulting from diabetes. Studies in galactose-fed rats are being conducted with scientists in the Ophthalmic Division, Osaka Prefectural Hospital. This study has demonstrated a decreased tactile sensitivity of the central cornea in the galactose-fed rat model of diabetic complications. This model could be useful for investigating the pathogenic mechanism(s) involved in decreased corneal sensitivity associated with diabetic keratopathy. Other Laboratory scientists are pursuing joint studies on the role of aldose reductase in diabetes-induced loss of corneal sensitivity and the ameliorative effects of aldose reductase inhibitors such as CT-112.

Investigators in the Laboratory of Molecular and Developmental Biology are cooperating with a scientist at RIKEN Institute, who from 1992 through 1995 was a Postdoctoral Fellow in the Laboratory's Regulation of Gene Expression Section. This joint project continues the research on the transcription factor AP2 alpha, which was started at NEI. The work characterized a novel splicing variant in the ocular lens that may have a role in regulating gene transcription in the lens. The results of this research have been published.

Scientists in the Laboratory of Sensorimotor Research are working with a former colleague who is now at the Electrotechnical Laboratory, Tsukuba, on the role of the cortex in the generation of reflex eye movements that are important for stability of the retinal image.

Nepal

In collaboration with WHO and the Nepal Netra Jyoti Sangh, NEI's Deputy Director and the Associate Director for Applications of Vision Research have served on a technical advisory committee to oversee a survey of the prevalence of blindness and outcomes of cataract surgery in two areas of Nepal. The survey has involved eye examinations for 4,600 adults older than age 45 years, and it has provided information on the effect of more than 10 years of blindness prevention activities by several international nongovernmental organizations in Nepal. Results point to the need for improvements in reaching the visually impaired and in ensuring the best achievable outcome with cataract surgery.

Peru

A survey of the prevalence of blindness and the outcomes of cataract surgery has been conducted in Chimbote. Essentially replicating the Nepal protocol, this investigation is a collaboration of NEI, WHO, and Peru's National Institute of Ophthalmology, Lima.

Spain

NEI scientists from the Laboratory of Mechanisms of Ocular Disease are collaborating with researchers from the Universidad de Santiago de Compastela to investigate the precursor cells and mechanisms involved in diabetes-related retinal angiogenesis. The purpose of the study is to develop inhibitors of various growth factors that can be used to slow or stop the progress of this blinding condition of late-stage diabetic retinopathy.

Sweden

Many eye diseases, especially those resulting in retinal degeneration, could be successfully treated if transplantation of the human retina were possible. In animal models, transplanted visual cells do not develop and function normally. However, a new differentiating factor has been discovered and is being investigated by molecular biology techniques at NEI. This factor, a protein that causes neuronal-like differentiation, is being tested in vitro by NEI collaborators in Sweden at the University of Göteborg and the University of Lund, Malmö, to determine whether it will cause retinal cell differentiation. The ultimate purpose of these investigations is to develop cells that could be transplanted into the human eye and function there normally.

The Early Manifest Glaucoma Trial is a multicenter randomized clinical trial designed to determine whether treatment to reduce intraocular pressure in newly detected open-angle glaucoma affects progression of the disease. The primary purpose of the trial is to compare the effect of immediate treatment designed to lower intraocular pressure with the effect of late treatment or no treatment. Disease progression was measured by increasing loss of visual field, changes in the optic disc, or both. The secondary purposes of the trial are (a) to determine the extent of reduction of intraocular pressure resulting from treatment; (b) to explore factors that may influence the progression of glaucoma; and (c) to describe the natural history of newly detected glaucoma. Investigators at the University of Lund, Malmö, collaborating with investigators at the State University of New York, Stony Brook, have enrolled 255 patients with newly diagnosed disease. Participants have been randomly assigned either to receive treatment to lower pressure in the eye or to be observed and receive no treatment or delayed treatment. Patient recruitment began in 1993 and was completed in 1997. The investigators are using computerized perimetry and fundus photography for close, long-term follow-up of all patients.

United Kingdom

The United Kingdom Prospective Diabetes Study is a multicenter randomized clinical trial comparing different therapies, to determine whether improved control of blood glucose levels or blood pressure in non–insulin-dependent diabetes mellitus (type 2 diabetes) reduces morbidity and mortality. Starting in 1977, 5,102 patients with newly diagnosed type 2 diabetes were treated with diet therapy for 3–4 months. Patients who remained asymptomatic but had high blood glucose levels were then randomly assigned to diet therapy or to treatment with sulfonylurea, insulin, or metformin. In a factorial design, a randomized trial of strict control of blood pressure was carried out in 1,148 patients with type 2 diabetes and hypertension. Patients were assigned to treatment of hypertension with angiotensin-converting enzyme inhibitors or β-blockers or to less tight control of hypertension. All patients' eyes are photographed every 3 years to assess development and progression of diabetic retinopathy. The median duration of follow-up is 12 years.

Scientists in NEI's Laboratory of Mechanisms of Ocular Diseases are collaborating with investigators at the University of Cambridge, England, in a study on differentially expressed genes in the osteonectin (SPARC) knockout mouse. This mutation causes phenotypic expression of cataract in animals 6 months of age or older. The knockout mouse is a model for maturity-onset cataract. This study is designed to evaluate and identify early changes in gene expression that may account for the development of cataract.

Other scientists at this NEI Laboratory have begun to collaborate with investigators at the University of Dundee, Scotland, to study the heat shock proteins that may be altered in glaucoma. These investigators are using human trabecular meshwork cells to study how distention of the trabecular meshwork, the site of resistance to outflow of aqueous humor, may be related to changes observed in primary open-angle glaucoma.

Scientists at the Laboratory of Molecular and Developmental Biology are working with investigators at Baylor College of Medicine, Houston, Texas, and the Imperial Cancer Research Fund, London, England. These scientists are targeting the expression of the FGF3/int2 gene to the lens. This work will allow researchers to characterize the fibroblast growth factor (FGF) receptors that FGF3 interacts with and the role of secreted FGFs in differentiation in the lens. The scientists have published a report on this research.

Activities With International and Multinational Organizations

During FY 98, NEI continued to support investigations of blinding eye diseases that have a worldwide impact. These studies are implemented through (a) bilateral agree ments between foreign countries and the United States; (b) other types of country-to-country programs, such as those supported by the U.S. Agency for International Development; and (c) collaborative activities with WHO, the Pan American Health Organization, and foundations and private and voluntary organizations such as the Lions Clubs International Foundation.

NEI continues to provide technical advice to the Lions Clubs International Foundation in the development of its $100 million SightFirst initiative, a global sight-conservation program aimed at substantially reducing the prevalence and incidence of preventable and curable vision loss. In addition, the Associate Director for Applications of Vision Research continues to serve as a technical advisor for the Americas and to the SightFirst Program of the Lions Clubs International Foundation. This program has sponsored scores of cataract eradication projects involving about 20 countries in Central and South America.

During FY 98, NEI also continued its activities as a WHO Collaborating Center for the Prevention of Blindness. The NEI Director continued to serve on the WHO Special Advisory Panel in the Prevention of Blindness. The Director and the Associate Director planned new collaborative research protocols and methods, specifically for research on childhood blindness in developing countries, with the manager of the WHO Prevention of Blindness Program. In addition, other NEI staff members have, on request, acted as consultants to the WHO program.

NEI is working closely with nongovernmental organizations in designing service and research programs to reduce the prevalence of blindness, regardless of its cause, throughout the world. A special emphasis over the past 2 years has been the evaluation of program performance in selected countries. It is expected that this effort will continue for several years.

Extramural Programs

In FY 98, NEI made eight awards in support of investigator-initiated research projects in six countries. The clinical projects funded by NEI include the Early Manifest Glaucoma Trial, in Sweden, and the United Kingdom Prospective Diabetes Study (see also the section on "Country-to-Country Activities and Bilateral Agreements"), as well as clinic activities in Canada for the multicenter Collaborative Ocular Melanoma Study.

Basic research projects funded by NEI include the following investigations:

- Australia—examination of the role of growth factors in lens development and cataractogenesis, to investigate the relationship between specific growth factors and differentiation in the lens and to study the role of growth factors in cataract formation;
- Canada—efforts to improve functional magnetic resonance imaging technology through proof-of-performance imaging of ocular dominance columns in the human visual cortex and through investigation of the factors that control formation of photoreceptor cell synapses and gap junctions during developmental assembly in the retina;
- India—study of the mechanisms that control development of the lens, calcium homeostasis, and pigmentation, to provide insight into the causes of major forms of cataract;
- Israel—investigation of the molecular mechanisms of phototransduction and how defects in this signaling pathway can lead to retinal degeneration; and
- United Kingdom—investigation of calcium in the physiology of normal and cataractous lenses, by understanding the role that increased calcium levels in cataractous lesions may have on the development of cataract.

Before award, each of these foreign projects was specifically approved by the National Advisory Eye Council. This review is performed to ensure that these grants present special research opportunities with specific relevance to the mission and objectives of NEI.

International Meetings

In October 1997, the NEI Director and the Associate Director for Applications of Vision Research organized and lectured at a course on clinical trials, including the design, conduct, and interpretation of clinical trials. The course was targeted to the international membership at the American Academy of Ophthalmology, San Francisco, California.

In November 1997, the Associate Director cochaired and lectured at a Lions Clubs International Foundation SightFirst Regional Course on Prevention of Blindness and Eye Care Management, in Nakhon Ratchasima (Korat), Thailand.

In February 1998, the Director and the Associate Director were consultants to WHO, in Geneva, Switzerland, on the analysis of blindness prevention outcomes, particularly the chief findings of the evaluation of the national blindness prevention programs in both China and Nepal.

In March 1998, the Director and the Associate Director organized and lectured at a course on methods of clinical trial investigation at the Pan American Association of Ophthalmology, in Buenos Aires, Argentina.

In May 1998, the Group Leader, Epidemiology and Clinical Studies, presented a paper entitled Development and Validation of a Food Frequency Questionnaire in a Trial of Eye Diseases, at the Dietary Assessment Methods Conference, in Arnhem, the Netherlands.

In June 1998, the NEI Director and the Associate Director cochaired a seminar in quality-of-life assessment on cost-effectiveness analysis of cataract surgery, at the XXVIIIth International Congress of Ophthalmology, in Amsterdam, the Netherlands.

Intramural Programs and Activities

NEI continued to serve as an international center for research and training on eye disease. In FY 98, 22 Visiting Fellows, 3 Visiting Associates, 8 Visiting Scientists, 13 Special Volunteers, and 1 Guest Researcher, from more than 20 countries conducted research at NEI's intramural facilities in Bethesda, Maryland. Their work included basic laboratory investigations on the molecular structure and development of the visual system, sensory and motor disorders of vision, and the biochemical bases of retinal and corneal diseases and the development of cataract. In addition, Visiting Scientists collaborated with NEI investigators in clinical studies to define, prevent, and treat vision disorders, such as genetic and developmental defects, ocular inflammatory disease, and ocular complications due to systemic conditions such as diabetes.

XVI.
National Institute of General Medical Sciences

INTRODUCTION

The National Institute of General Medical Sciences (NIGMS) supports basic research and research training in the biomedical sciences. Although most of the research and research training are not disease oriented, NIGMS grantees contribute to the stores of new knowledge, theories, and ideas that form the foundation for the more disease-targeted investigations funded by other units of the National Institutes of Health (NIH). In addition, the NIGMS research training programs help to provide the most critical element required for outstanding research—well-prepared investigators with broad backgrounds in multidisciplinary research. Notable research projects of investigators in foreign countries receive support from this Institute exclusively within its extramural activities.

NIGMS began as the Division of General Medical Sciences in 1958 and became an Institute in 1962. In 1994, the Institute reorganized its research and training activities into four divisions. Three divisions award grants for research projects and research training—the Division of Cell Biology and Biophysics; the Division of Genetics and Developmental Biology; and the Division of Pharmacology, Physiology, and Biological Chemistry. The Division of Minority Opportunities in Research funds research and research training grants to colleges and universities with high minority enrollments, through the Minority Access to Research Careers Branch and the Minority Biomedical Research Support Branch, respectively. The Division of Minority Opportunities in Research also administers the Bridges to the Future Program for the NIH Office of Research for Minority Health. This Division does not participate in the Institute's international activities.

Division of Cell Biology and Biophysics

The Division of Cell Biology and Biophysics focuses its resources on application of the research principles of basic physics and engineering sciences to biology. Its goal is to gain a greater understanding of the structural and functional relationships of cells, cellular constituents, and the constituent macromolecules that, in concert, form these cellular organelles. Studies supported by the Division consist of (a) basic research on the structure, function, and interaction of proteins and biopolymers and (b) investigation of the properties and functions of cellular elements. The ultimate goal is to prevent, treat, and cure diseases resulting from disturbed or abnormal cellular activity. The Division has two components: the Cell Biology Branch and the Biophysics Branch.

The Cell Biology Branch supports investigations related to the fundamental questions involving the function, structure, and regulation of cells, as well as the role of cellular dysfunction in disease. Problems addressed range from macromolecular assembly of cellular components to cellular motility and adhesion. The areas of study include

- plasma and intracellular membranes, receptors, and signal transduction mechanisms;
- structure and function of the cytoskeleton;
- mechanisms of cell motility and cell division;
- regulation of protein and membrane synthesis and activation of cell growth;
- subcellular organelles and their role in cellular integrity; and
- biochemistry, cell biology, and biophysics of lipids, lipid synthesis, and lipid interactions.

The Biophysics Branch funds research in the areas of biophysics and bioengineering disciplines that use techniques derived from the physical sciences to examine the structure and properties of biological substances. This research includes

- determination of the structure of proteins and nucleic acids;
- study of the structural features that determine macromolecular conformation;
- structural analysis of macromolecular interactions and ligand–macromolecular interactions;
- development of methods for and pilot studies of structural genomics;
- development of physical methods for analysis of molecular structures;
- development and use of theoretical methods to investigate biological systems; and
- fostering of bioengineering research on development and refinement of all forms of instruments and methods, bioanalytic techniques, and biomaterials needed to conduct research in the biological sciences.

Through National Research Service Awards (NRSAs), the Division maintains predoctoral institutional training grants and individual postdoctoral fellowships in biophysics, areas related to the chemistry–biology interface, and cellular and molecular biology. The Division also provides for research training of physician-scientists through the Medical Scientist Training Program, a combined medical and research doctoral (M.D./Ph.D.) training activity.

Division of Genetics and Developmental Biology

The Division of Genetics and Developmental Biology supports studies directed toward gaining a better understanding of the fundamental mechanisms of inheritance, development, and cell function. The findings of these studies contribute to the more targeted research projects supported by other NIH components. Most of the projects supported by the Division make use of nonhuman model systems. It is expected that the results of these investigations will lead to the eventual diagnosis, prevention, therapy, or cure of human genetic and developmental disorders. Among the areas under investigation are

- regulation of gene expression;
- replication, repair, and recombination of DNA;
- RNA processing;
- protein synthesis;
- extrachromosomal inheritance;
- population genetics and evolution;
- developmental genetics;
- cell-cycle control and cell growth and differentiation;
- chromosomal organization and mechanics and rearrangement of genetic elements; and
- neurogenetics.

The Division also supports NRSA predoctoral training grants and individual postdoctoral fellowships, as well as one research resource, the Human Genetic Mutant Cell Repository.

Division of Pharmacology, Physiology, and Biological Chemistry

The Division of Pharmacology, Physiology, and Biological Chemistry supports a broad spectrum of research and research training aimed at improving understanding of fundamental biological processes at the molecular level and discovering approaches to their control. The Division supports research projects involving a multifaceted approach to problems in pharmacology, physiology, biochemistry, and biorelated chemistry that are basic in nature or that have implications for more than one disease area. The Division has two components: the Biochemistry and Biorelated Chemistry Branch and the Pharmacological and Physiological Sciences Branch.

The areas of research supported by the Biochemistry and Biorelated Chemistry Branch include

- enzyme catalysis and regulation and intermediary metabolism;
- bioenergetics and redox biochemistry and glycoconjugate chemistry;
- bioinorganic chemistry and electron transport and energy transduction;
- organic synthesis and methods and medicinal chemistry;
- synthesis of natural products, structure and function of small molecules, and development of new medicinal agents, including agents that mimic macromolecular functions;
- drug discovery and design; and
- biotechnology (biological catalysis and control processes).

The areas of study supported by the Pharmacological and Physiological Sciences Branch include

- drug actions and mechanisms of anesthesia;
- new methods and targets for drug discovery;
- interactions of drugs with endogenous mediators of physiological responses;
- drug metabolism, drug-delivery strategies, and bioavailability;
- regulation and pharmacological manipulation of receptors and channels, secondary and tertiary messenger systems, and mediator molecules;
- pharmacogenetics;
- total-body biochemical and physiological response to trauma and burns;
- etiology of post-traumatic sepsis and the mechanisms of immunosuppression, wound healing, and hypermetabolism; and
- molecular immunobiology.

The Division funds NRSA predoctoral institutional training grants in the pharmacological sciences and biotechnology, as well as the study of systems and integrative biology. This Division also funds postdoctoral institutional research training grants in clinical pharmacology and anesthesiology and in trauma and burn injury; individual postdoctoral fellowships; and the Pharmacology Research Associates Program, a postdoctoral fellowship program in the NIH intramural arena.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCED RESULTING FROM INTERNATIONAL ACTIVITIES

DNA–Protein Complex of *Bacillus subtilis* Bacteriophage

Scientists at NIGMS have been studying the mechanism of protein-primed DNA replication in the model bacteriophage phi29 of *Bacillus subtilis*. Health-related viruses such as adenovirus and hepatitis B virus replicate by similar protein-priming mechanisms. The long-term objective of the research is to find specific ways to interfere with viral replication.

HIV-1 gp120

NIGMS, in collaboration with the Weizmann Institute of Science, Rehovot, Israel, ascertained the three-dimensional structure of a major antigenic determinant of the HIV-1 gp120 (glycoprotein 120) bound to a fragment of the neutralizing antibody. Surprisingly, the same determinant regions from two HIV-1 isolates have significantly different structures, which may correspond to the inactive and active forms of gp120. The interconversion of these two forms may be one role of immunophilins in HIV-1 infection.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Extramural Programs

Human Genetic Mutant Cell Repository

The NIGMS Human Genetic Mutant Cell Repository provides a valuable resource for investigators studying genetic disorders. It is located at the Coriell Institute for Medical Research, Camden, New Jersey. The repository collects, characterizes, maintains, and distributes cell lines from patients with a wide variety of genetic disorders and from healthy persons whose tissue serves as controls. Approximately 6,600 cell lines representing more than 350 diseases are available to qualified investigators. DNA samples from more than 1,300 of these cell lines are also available.

Cell lines in the repository are used for biochemical, cellular, and molecular studies to help elucidate the causes of genetic defects. In addition, the repository supplies DNA samples isolated from human–rodent somatic cell hybrids that are well characterized. Two complete panels are available for whole-genome mapping, and a growing number of chromosome-specific somatic cell hybrid panels are also available. The hybrids are a valuable resource to investigators interested in determining the location of disease-related genes.

Also, the repository has acquired from Centre d'Etude du Polymorphisme Humain, Paris, France, approximately 800 cell lines from 60 families. The cell lines have been used for gene-mapping studies by a group of collaborators around the world. The availability of these cell lines in the repository will greatly increase the access to this valuable resource and will also enable investigators, for the first time, to obtain the cell lines as well as DNA derived from them. Investigators working outside the United States purchase approximately 20% of the cell culture and DNA samples that are distributed each year.

Foreign Research Grants

Principal investigators in appropriate research establishments in foreign countries are eligible to submit grant applications for research projects to the NIH. During fiscal year 1998, NIGMS funded 10 grants to principal investigators in four countries (Argentina, Canada, Israel, and Spain) and supported four Postdoctoral Fellows in three countries (Canada, France, and the United Kingdom).

International Meetings

NIGMS joined other NIH Institutes in providing support for participation of U.S. and foreign scientists in the 6th International Conference on Biophysics and Synchrotron Radiation, in Chicago, Illinois, and the 6th International Conference on Intelligent Systems for Molecular Biology, in Montreal, Quebec, both in July 1998.

XVII.
National Heart, Lung, and Blood Institute

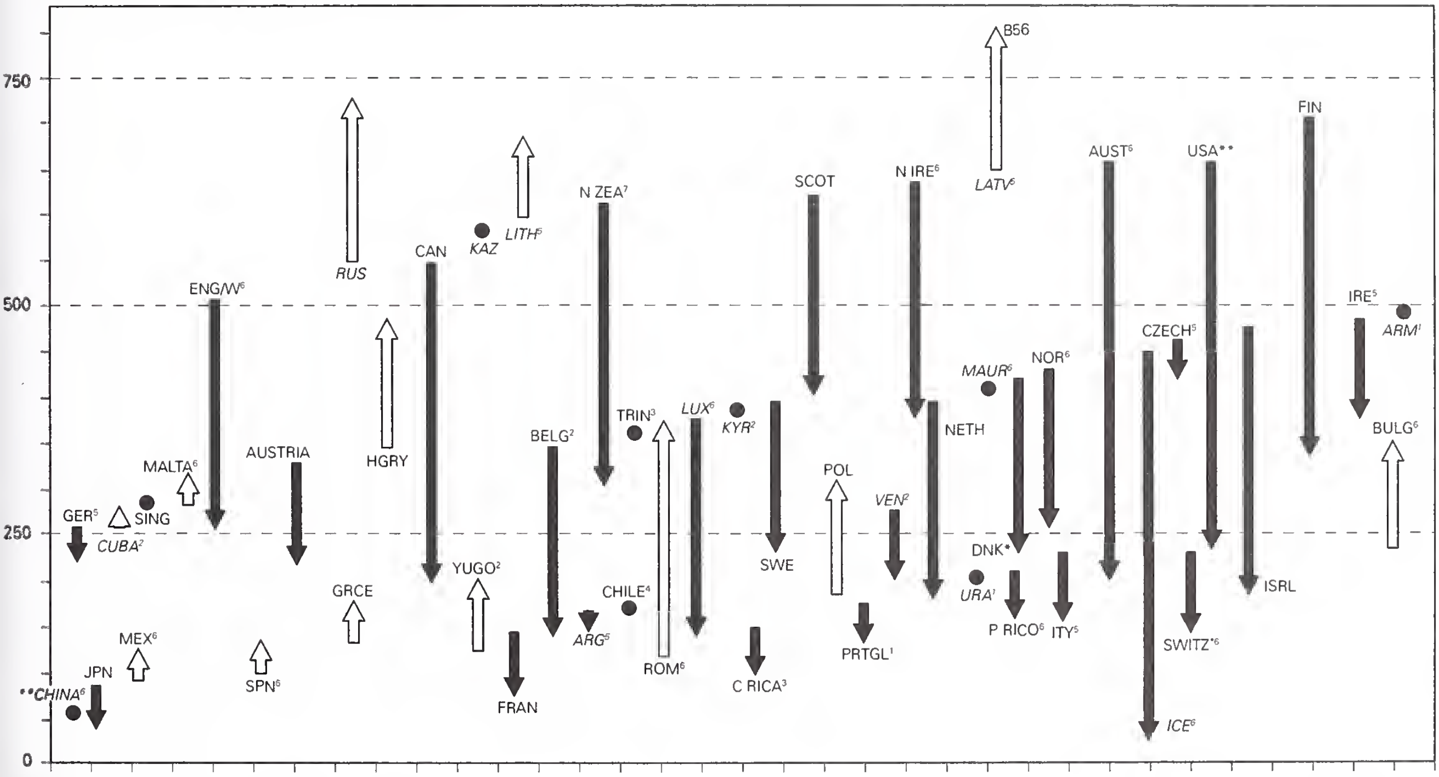
INTRODUCTION

Global communications and rapid transfer of technology are transforming medicine and science. The National Heart, Lung, and Blood Institute (NHLBI) is playing a leadership role in international health policy and in transferring and applying new knowledge to prevent and control heart, lung, and blood diseases. Fiscal year 1998 (FY 98) represented a milestone in the history of the Institute, as NHLBI celebrated 50 years of service to the American people and populations throughout the world. Thousands of scientists, physicians, health educators, technologists, ethicists, and economists from the United States and other countries have contributed to the NHLBI programs. Major professional organizations in the United States and international organizations, such as the World Health Organization (WHO) and the Pan American Health Organization (PAHO), have also contributed. Additionally, the biotechnology and pharmaceutical industries have collaborated with the Institute in the development of drugs and devices.

During FY 98, the Institute continued to expand its international contacts with WHO and PAHO, as a WHO Collaborating Center for Cardiovascular Research and Training for the Americas, as well as with other international organizations. The international programs continued to undergo changes in direction and emphasis, to take advantage of new opportunities. Over the last few decades, cardiopulmonary diseases have been one of the most intensively studied areas in biological science. Major advances in cellular, molecular, and gene technology, such as DNA sequencing, identification of

FIGURE XVII-1.

Death Rates for Coronary Heart Disease by Country for Men Ages 35–74 Years, 1970 and 1995



Rate per 100,000 population. Age adjusted to European Standard Population.

*Rates are based on *International Classification of Diseases*, 8th revision (ICD-8) for Switzerland (SWITZ) and 9th revision (ICD-9) for Denmark (DNK).

**Rate is for rural areas of China. Rate for urban areas was 99.6 per 100,000 population.

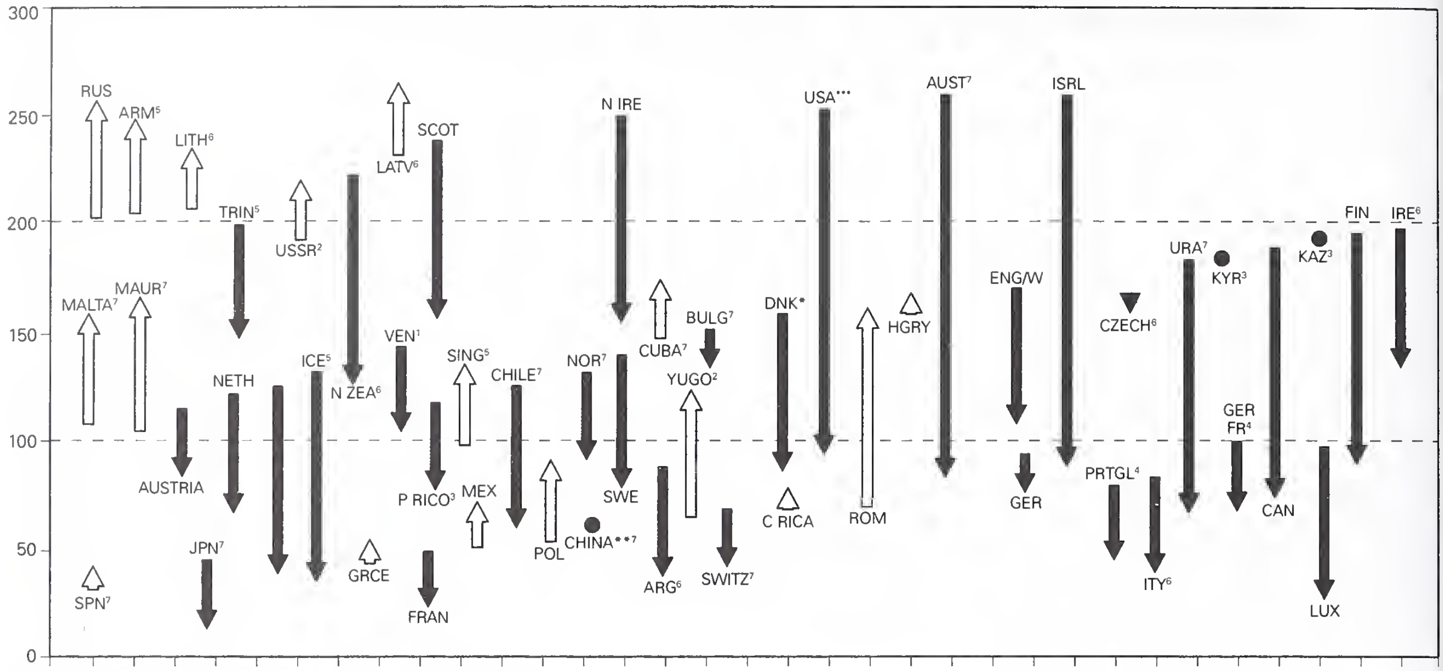
***Rates for the United States (USA) are based on *Public Use Mortality Data Tapes*, National Center for Health Statistics, Centers for Disease Control and Prevention, 1992.

Source: *World Health Statistics Annual. WHO* (selected issues).

[1] 1970 and 1971
[2] 1970 and 1990
[3] 1970 and 1991
[4] 1970 and 1992
[5] 1970 and 1993
[6] 1970 and 1994

FIGURE XVII-2.

Death Rates for Coronary Heart Disease by Country for Women Ages 35–74 Years, 1970 and 1995



Rate per 100,000 population. Age adjusted to European Standard Population.

*Rates are based on *International Classification of Diseases*, 9th revision (ICD-9) for Denmark (DNK).

**Rate is for rural areas of China. Rate for urban areas was 69.0 per 100,000 population.

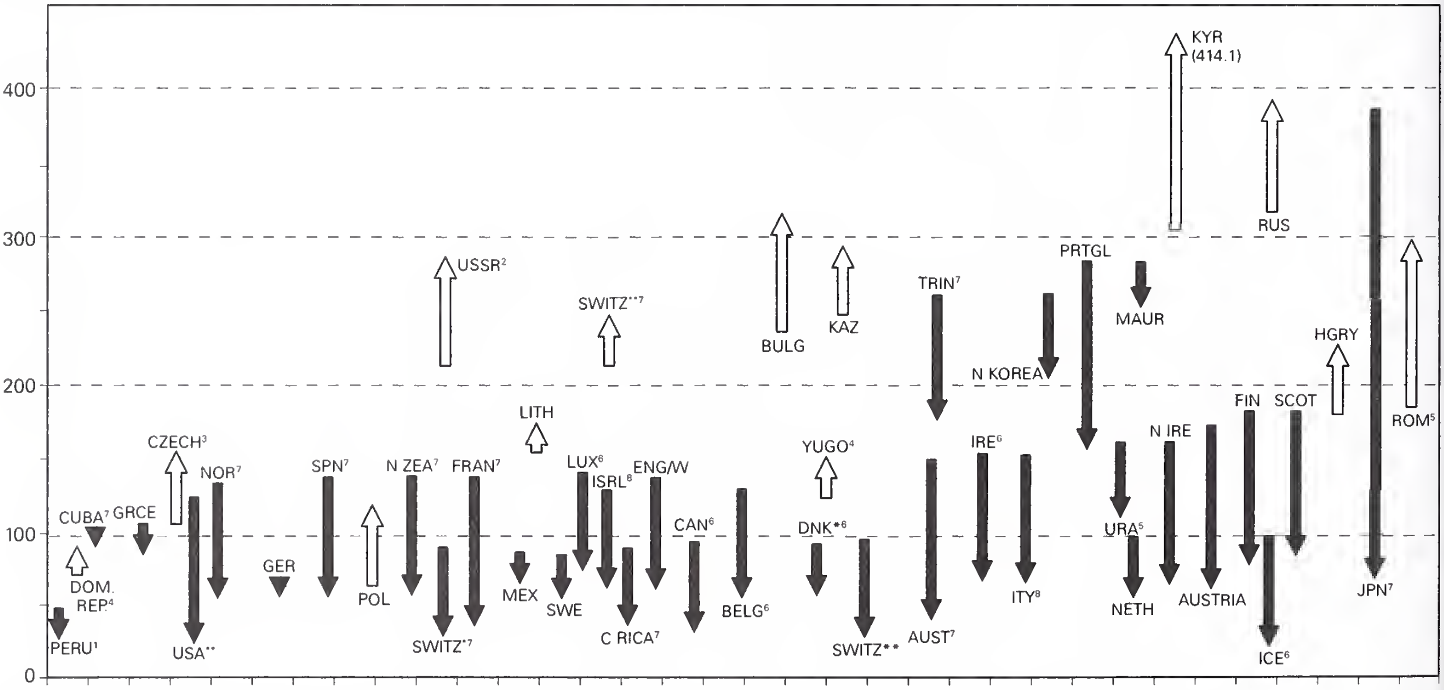
***Rates for the United States (USA) are based on *Public Use Mortality Data Tapes*, National Center for Health Statistics, Centers for Disease Control and Prevention, 1992. Rates in 1992 are based on ICD-9.

Source: World Health Statistics Annual. WHO (selected issues).

[1] 1970 and 1989
[2] 1970 and 1990
[3] 1970 and 1991
[4] 1973 and 1971
[5] 1970 and 1992
[6] 1970 and 1993
[7] 1970 and 1994

FIGURE XVII-3.

Death Rates for Stroke by Country for Men Ages 35–74 Years, 1970 and 1995



Rate per 100,000 population. Age adjusted to European Standard Population.

*Rates are based on *International Classification of Diseases*, 8th revision (ICD-8), for Switzerland (SWITZ) and 9th revision (ICD-9) for Denmark (DNK).

**Rates are for rural areas of China. Rates for urban areas were 246 and 251 per 100,000 population.

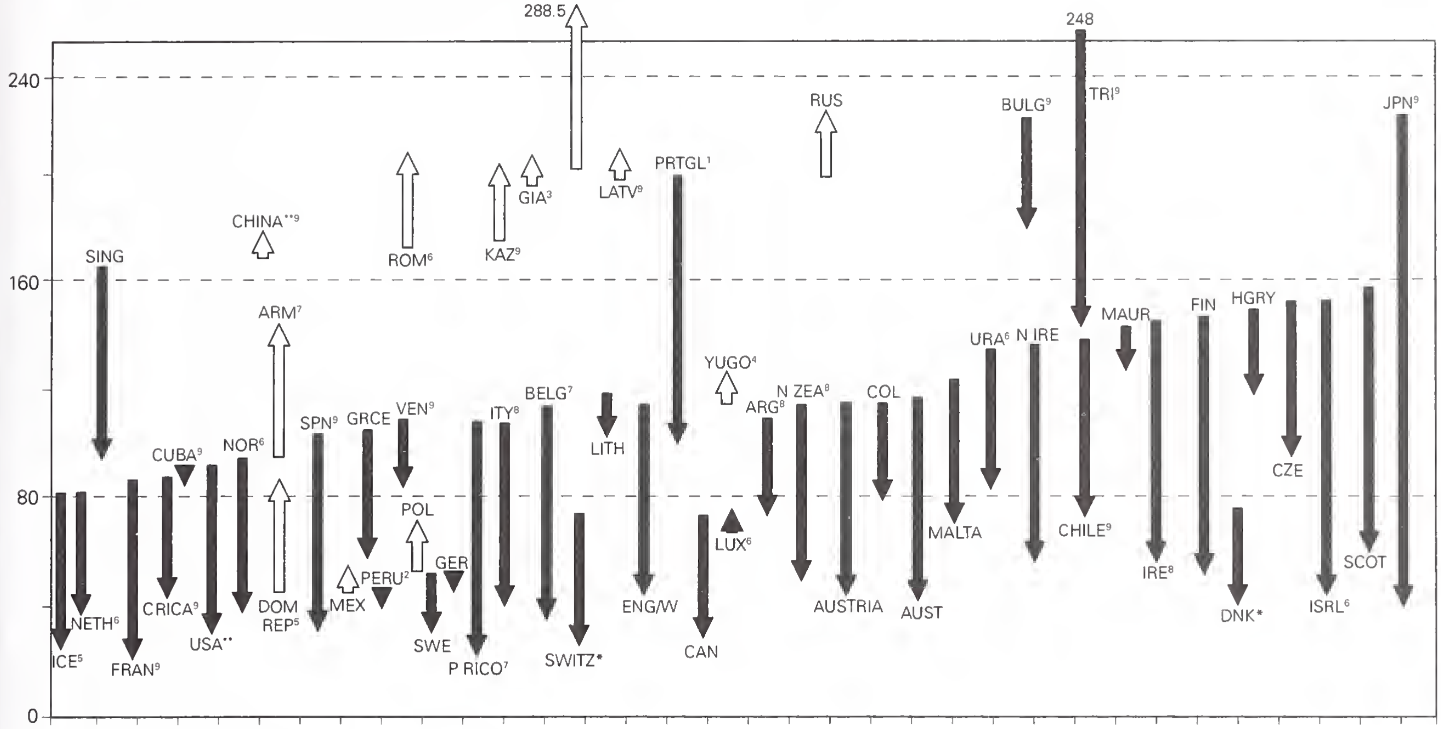
***Rates for the United States (USA) are based on *Public Use Mortality Data Tapes*, National Center for Health Statistics, Centers for Disease Control and Prevention, 1992.

Source: World Health Statistics Annual. WHO (selected issues).

[1] 1970 and 1983
[2] 1970 and 1990
[3] 1970 and 1991
[4] 1971 and 1982
[5] 1973 and 1990
[6] 1970 and 1992
[7] 1970 and 1994

FIGURE XVII-4.

Death Rates for Stroke by Country for Women Ages 35–74 Years, 1970 and 1995

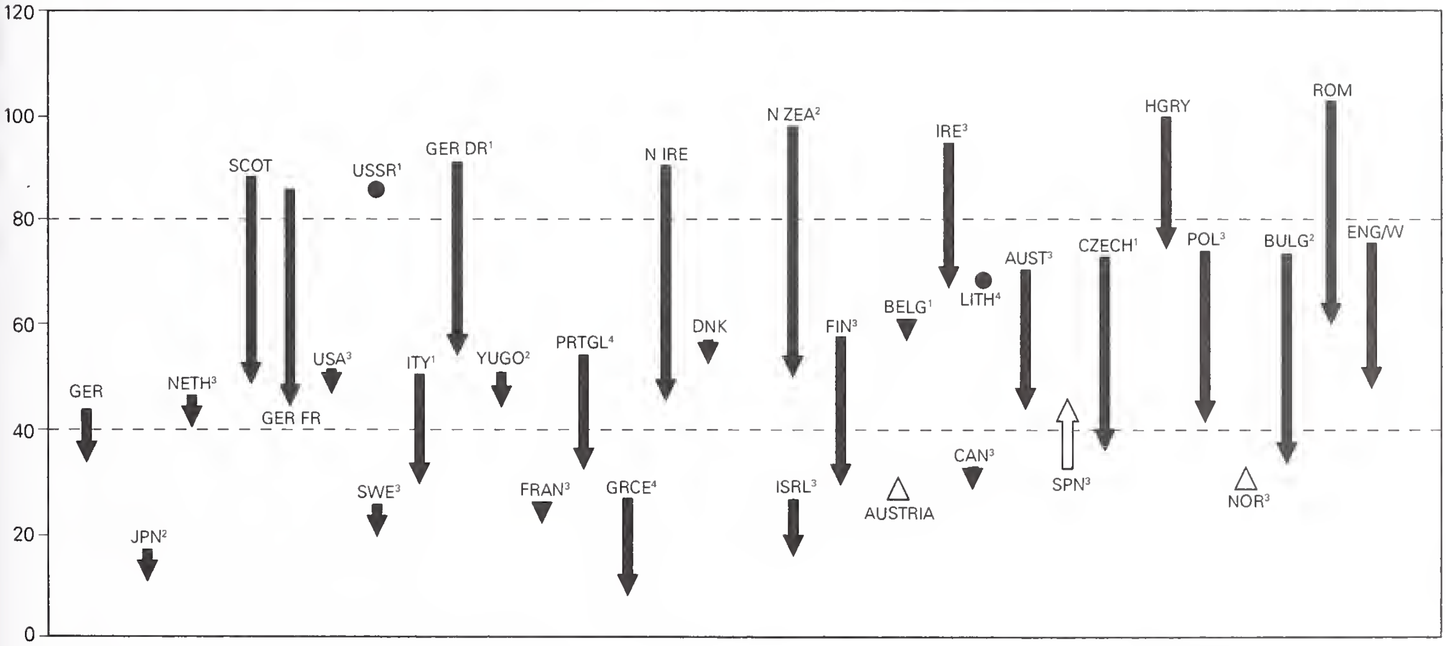


Rate per 100,000 population. Age adjusted to European Standard Population.
*Rates are based on *International Classification of Diseases*, 8th revision (ICD-8) for Switzerland (SWITZ) and 9th revision (ICD-9) for Denmark (DNK).
**Rates are for urban areas of China. Rates for rural areas were 148.3–151.3 per 100,000 population.
***Rates for the United States (USA) are based on *Public Use Mortality Data Tapes*, National Center for Health Statistics, Centers for Disease Control and Prevention, 1992.
Source: World Health Statistics Annual. WHO (selected issues).

[1] 1970 and 1971
[2] 1970 and 1983
[3] 1970 and 1989
[4] 1970 and 1990
[5] 1971 and 1982
[6] 1973 and 1990
[7] 1970 and 1992
[8] 1970 and 1993
[9] 1973 and 1994

FIGURE XVII-5.

Death Rates for COPD and Allied Conditions by Country for Men Ages 35–74 Years, 1980 and 1997

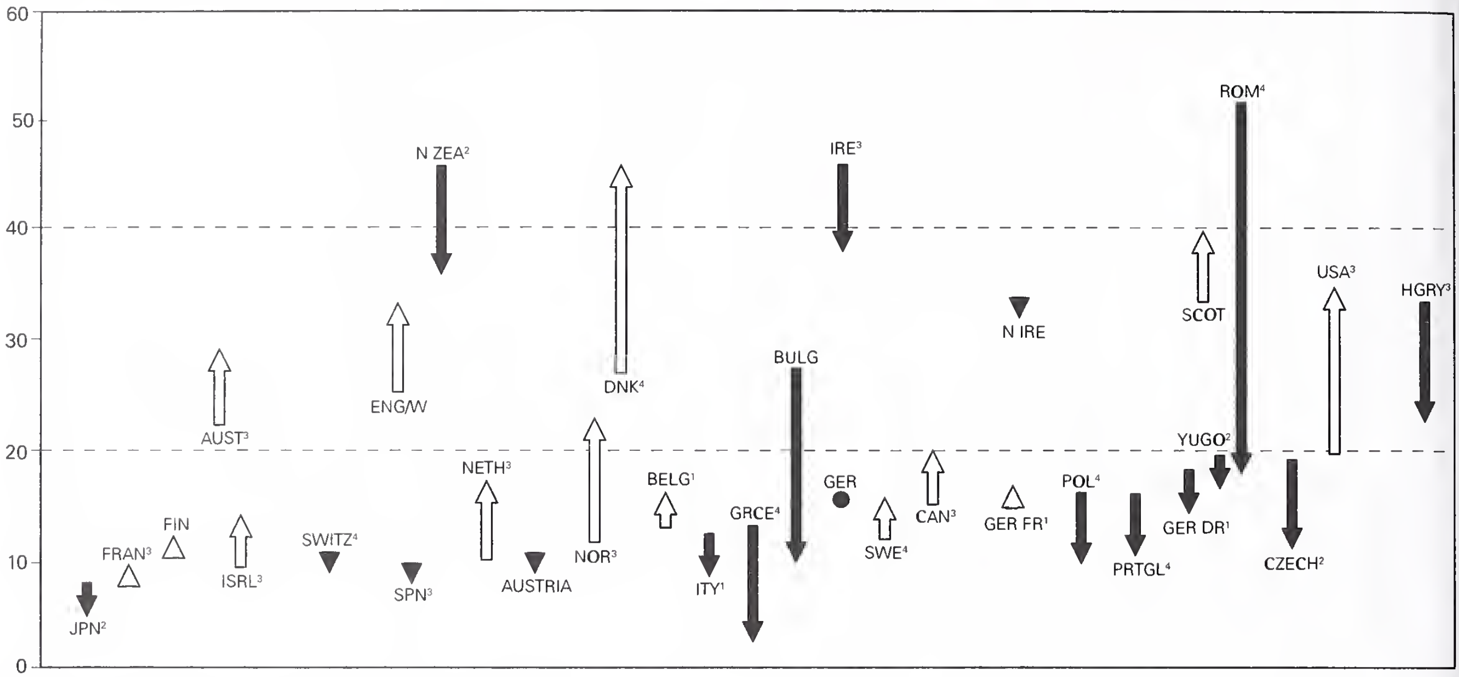


Rate per 100,000 population. Age adjusted to European Standard Population.
International Classification of Diseases, 9th Revision (ICD-9), codes 490–496.
Source: World Health Statistics Annual, WHO. Unpublished.

[1] Updated to 1993
[2] Updated to 1994
[3] Updated to 1995
[4] Updated to 1996

FIGURE XVII-6.

Death Rates for COPD and Allied Conditions by Country for Women Ages 35–74 Years, 1980 and 1997



Rate per 100,000 population. Age adjusted to European Standard Population.
International Classification of Diseases, 9th Revision (ICD-9) codes 490–496.
Source: World Health Statistics Annual, WHO. Unpublished.

[1] Updated to 1993
[2] Updated to 1994
[3] Updated to 1995
[4] Updated to 1996

disease genes, and special techniques, are rapidly expanding our knowledge. These new developments are reflected in NHLBI's international collaborations, focusing on research of mutual interest and benefit.

As indicated in previous reports on NHLBI's international activities, there is a growing worldwide pandemic of cardiopulmonary disease, especially in developing countries. Marked international differences in death rates and trends of cardiovascular and pulmonary diseases, as seen in Figures XVII-1 through XVII-6, continue to raise important scientific questions and provide new challenges for international collaboration to explore the reasons for these differences and to develop scientific partnerships to prevent and control these diseases. Two reports were jointly authored by WHO, the Harvard School of Public Health, Boston, Massachusetts, and the World Bank in 1996: *The Global Burden of Disease* and *Global Health Statistics*. These reports predict major changes in global patterns of disease. By the year 2020, it is anticipated that noncommunicable diseases such as heart and lung diseases will be the number one global disease burden, as deaths and disabilities from malnutrition and infection continue to decline. These data have direct implications for future NHLBI international programs. They serve to stimulate an even greater commitment to search for more effective approaches to prevent, control, and treat these diseases and to relieve the suffering of millions. According to WHO, cardiovascular disease (CVD) alone is responsible for more than 12 million deaths each year and hundreds of billions of dollars in economic losses.

At the same time, new solutions are being developed through advances in scientific knowledge and public health action to promote health and control disease through evidence-based programs of international scope. Rapidly advancing information technologies are having a dramatic impact on the sharing of information and data in biomedical collaboration. These new approaches are making it possible for scientists and physicians to retrieve, store, transmit, and analyze data in totally new ways. For the first time in the history of medicine, scientists in different parts of the world have the capability to instantly pool and review data on a global basis, from joint studies in basic, clinical, and epidemiologic research. These advances are having major impacts on international collaboration in medicine and science. Technologies under development include telecommuting, teleconferencing, and teleconsultation. Computers, satellite connections, the World Wide Web, and multimedia approaches are being used to facilitate global collaboration in cardiovascular and pulmonary research.

The Institute's current international collaborations cover the entire research spectrum, including basic research, applied research and development, clinical investigation, population-based studies, demonstration and education, and training and development. The international programs build on national research efforts in priority areas included in the National Heart, Blood Vessel, Lung, and Blood Program Plan developed by NHLBI in collaboration with committees of extramural advisors. Table XVII-1 shows how the international programs intersect with these national programs.

TABLE XVII-1.

National Heart, Lung, and Blood Institute: International Activities, Fiscal Year 1998

	Arteriosclerosis	Hypertension	Cerebrovascular Disease	Coronary Heart Disease	Arrhythmias	Heart Failure and Shock	Cardiomyopathies and Infections of the Heart	Pulmonary Cell Biology	Chronic Obstructive Pulmonary Diseases	Pediatric Pulmonary Diseases	Occupational and Immunologic Lung Diseases	Respiratory Failure	Pulmonary Vascular Diseases	Bleeding and Clotting Disorders	Disorders of the Red Blood Cells	Blood Resources	AIDS
Australia	●			●													
Canada	●			●	●				●	●		●					
China	●	●	●	●					●		●						
Czech Republic	●	●		●					●								
Egypt		●															
France	●			●				●			●		●				
Georgia	●	●															
Germany	●	●	●	●					●		●						
Hungary				●	●												
India			●														
Italy	●	●		●				●	●	●							
Japan	●	●	●	●					●								
Korea				●													
Kyrgyzstan								●	●								
Pakistan		●		●													
Poland	●	●	●	●	●		●		●								
Russia	●	●	●	●	●	●		●	●	●		●	●	●		●	
South Africa		●															
Uganda																	●
Vietnam															●		

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Recent highlights from joint international activities conducted with the support of NHLBI during FY 98 include collaboration with PAHO, WHO, and the Fogarty International Center (FIC) in organizing the first international conference addressing the CVD pandemic in the Western Hemisphere; partnering with South Africa in holding a Joint U.S.-South African Workshop on Hypertension in Blacks; support for major international resources in nutrition research; and planning for the G7-G8 Cardio Project with member countries. Also, as indicated in last year's report, NHLBI is continuing its participation in the Global Initiative for Asthma.

PAHO-WHO-NHLBI-FIC Conference on the Pandemic of Cardiovascular Disease

During FY 97, the Institute initiated the planning for the first joint international conference, held in May 1998, to focus attention on the global shifts in disease burden, specifically as these trends relate to the CVD pandemic in the Western Hemisphere. The conference also recognized the 50th anniversaries of WHO and NHLBI. The meeting was cochaired by the Directors of PAHO, NHLBI, and FIC. It provided a forum for representatives from ministries of health and scientific leaders from the Caribbean and Central, North, and South America to discuss the costs and challenges of the shifting global burden of disease and to jointly consider opportunities for initiatives to prevent and treat CVD in the Americas. As a direct result of this conference, NHLBI and PAHO have proposed a Pan American Hypertension Initiative. This proposal will be further discussed during a joint meeting in March 1999 of potential partners in the Americas. This initiative has the potential of impacting the health of 140 million hypertensives in the Western Hemisphere.

TABLE XVII-2.

National Heart, Lung, and Blood Institute: International Programs, Direct Costs for Fiscal Year 1998

	Number	Countries	Funds paid (in dollars)
Fellowship	1	United Kingdom	25,000
Grants	6	Canada	1,567,617
	4	United Kingdom	550,462
Cooperative Agreements	2	Canada	115,650
Total Awards	13		2,258,729
Centers for Disease Control and Interagency Agreement	1	China Pakistan Poland Russia	56,000
University of North Carolina Contract	1	China Pakistan Poland Russia	578,700
Bilateral Agreements[a]	17		375,575

Collaborating countries pay for the costs in their own country.

[a] Activities paid for by the National Heart, Lung, and Blood Institute.

U.S.-South African Workshop on Hypertension

The rapid socioeconomic changes occurring in South Africa are contributing to changes in the health of that nation, and a CVD epidemic is imminent. The United States has faced a similar situation in the past, and NHLBI and South African officials and scientists are collaborating on the development of plans to better cope with CVD in blacks in the United States and South Africa. A U.S.-South African Workshop on Hypertension in Blacks was hosted by NHLBI, in Bethesda, Maryland, in July 1998. Key U.S. and South African investigators pursued discussions on research topics of mutual interest and developed collaborative plans to better understand and address hypertension in black populations.

International Resources in Nutrition Research

NHLBI supports two important resources used in nutrition research in the United States, as well as in other countries. The University of Minnesota Nutrition Data System is an automated dietary interview method linked to data on the content of 92 nutrients in 16,000 brand-name food items. The system is in use, either directly or in modified versions, in several NHLBI international collaborative studies, including studies in cardiopulmonary epidemiology in China and the Intermap international blood pressure study in China, England, Japan, and the United States. NHLBI also supports the efforts of the U.S. Department of Agriculture to generate analytic data for the U.S. National Food Composition Data Base. These chemical analysis data are an international research resource, because they represent the world's largest single source of primary information on the nutrient content of foods and are used by many other countries that do not have the resources to establish their own databases.

G7-G8 International Cardio Project

Health telematics is rapidly transforming medicine. NHLBI and the National Library of Medicine are collaborating with technical groups from G7 and G8 countries in the planning of an International Cardio Project. It is proposed that this project would use the global application of health telematics to cardiology in developing a network for use by cardiologists and physicians. The proposed aims of the project are to develop a coordinated action among member countries to share technical solutions and to prepare the way for sharing patient databases in the future.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

The NHLBI international programs and activities are carried out within the mandates of the National Heart, Blood Vessel, Lung, and Blood Program. The direct costs for NHLBI international activities for FY 98 are summarized in Table XVII-2. During FY 98, NHLBI conducted activities with Australia, Canada, China, the Czech Republic, Egypt, Georgia, Germany, Hungary, India, Italy, Japan, Korea, Kyrgyzstan, Pakistan, Poland, Russia, South Africa, Uganda, and Vietnam.

Australia

NHLBI collaborates with Australia in an agreement between NHLBI and the Baker Medical Research Institute (BMRI), Victoria. This cooperation began with a number of visits to NHLBI by health administrators from the Australian Commonwealth, Department of Human Services and Health. In 1989, the Coordinator, and in December 1991, an epidemiologist from the South Australia Health Commission, Adelaide, visited NHLBI to share knowledge in cardiopulmonary disease prevention and care. These visitors expressed interest in NHLBI's successful approaches to disease prevention, which may be applicable to populations in Australia.

In May 1994, the head of an evaluation unit, Drug Evaluation Branch, Therapeutic Goods Administration, visited NHLBI to discuss mutual interests with the Director of NHLBI's Office of Prevention, Education, and Control and with staff of the Division of Heart and Vascular Diseases. The visitor expressed interest in recent studies on lipid disorders, hypertension, angina, myocardial infarction, and congestive heart failure; clinical trials; and new research approaches, particularly in relation to drug therapies and the control of drugs in the United States.

In June 1997, the Director, BMRI, visited NHLBI to discuss a mutually beneficial bilateral program of scientist exchanges. As a result, an agreement was made between NHLBI and BMRI to initiate such a program. Starting in September 1997, a senior principal research fellow of the Vascular Biology Laboratory, BMRI, collaborated for 4 months with a scientist in the Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, in basic research on molecular genetics. They are developing canine–human von Willebrand factor (VWF) chimeras in order to map the VWF binding sites and those of inhibitory antibodies.

In addition, in October 1997, the senior research officer, Lipoprotein and Atherosclerosis Laboratory, BMRI, worked with a professor of cardiovascular physiology at the Cardiovascular Research Institute (CVRI), University of California, San Francisco, in joint studies of molecular genetics. The Australian scientist's expertise in research on intracellular cholesterol trafficking and the role of apolipoprotein A-1 in cholesterol homeostasis complemented and enhanced the CVRI researcher's current investigations. These studies on interactions of platelets with the vessel wall are important in understanding the mechanisms of atherosclerosis. This joint experimental work overcame major methodological hurdles and generated new inquiries and methods of experimentation, providing the basis for continuing collaboration between CVRI and BMRI.

Also during FY 98, an associate professor of medicine at Baylor College of Medicine, Houston, collaborated with a researcher in the Vascular Biology Laboratory, BMRI. They worked on the molecular interactions between platelets and the vessel wall, including binding reactions between the P-selectin receptor on the endothelial surface and the glycoprotein Ib-X-V complex on platelet surfaces. The Australian scientist provided expertise in platelet biology, complementing U.S. expertise in molecular and cell biology of the endothelium and in an NHLBI-supported project on the structure and function of this glycoprotein complex.

The Director, NHLBI, participated in the Baker-Chang-Christ Church-Heart Institute Symposium, in Prahran, Victoria, in August 1998. This symposium was a joint meeting of scientists from Australia, New Zealand, and the United States. The symposium covered important and timely topics on CVDs of high priority to the participating countries and confirmed a continuing interest in joint collaborations between NHLBI and Australia.

Canada

Several clinical trials supported by NHLBI are carried out in collaboration with research groups in Canada. These trials are based on protocols that specify precise interventions and end points and validate new prevention and treatment regimens before these are introduced into medical practice. The requirement for large patient populations often makes these studies expensive and difficult to carry out. Collaboration with research centers in other countries enables NHLBI to maximize the information obtainable from a finite patient pool, reduce costs, and most important, make valid comparisons of results in different populations. During FY 98, Canadian scientists participated in the NHLBI studies presented here.

Bypass Angioplasty Revascularization Investigation

The Bypass Angioplasty Revascularization Investigation is assessing the relative safety and efficacy of percutaneous transluminal coronary angioplasty and coronary artery bypass graft (CABG) surgery in patients with multivessel disease and severe angina or ischemia who require revascularization and have coronary anatomy suitable for either procedure. Thirteen clinical centers, one of which is Canadian, and three coordinating centers are participating in this trial. The program was initiated in FY 87. Recruitment ended in August 1991. Follow-up has been extended until 2003. (For additional information about this trial, see also the subsection on "Czech Republic.")

Lung Health Study II

A previous study of early intervention for chronic obstructive pulmonary disease (COPD) in nine U.S. centers and one Canadian center was designed to determine whether special care is more effective than referral to usual care in slowing the rate of decline of pulmonary function in a population of smokers with mild abnormalities in pulmonary function. This study was merged into the Lung Health Study II, which aims to determine whether patients with COPD assigned to inhaled corticosteroid treatment have a lower rate of decline of pulmonary function and lower incidence of respiratory morbidity than similar patients assigned to placebo treatment. Ancillary studies include the effect of inhaled corticosteroids on adrenal sufficiency, bone mineral density, and osteocalcin levels. The study is scheduled to end in the fall of 1999.

Clinical Centers for Childhood Asthma Management Program

The primary objective of the Clinical Centers for Childhood Asthma Management Program is to determine, in a population of 5- to 9-year-old children with asthma, whether regular use of either of two classes of anti-inflammatory medications (inhaled corticosteroids or cromolyn sodium), compared with regular bronchodilator medication and with each other, resulted in greater lung function and less bronchial hyperresponsiveness over a 5-year period. The total enrollment is 1,041 children, including 123 from Toronto, Ontario. Follow-up is in progress for this double-blind study scheduled for completion in 1999.

During FY 98, a grant was awarded to McGill University, Montreal, Quebec, for a joint project on translational control of fibroblast viability, under the Specialized Centers of Research program. The objective of this joint research is to develop basic and clinical insights that can serve as the basis for improved therapies for patients with acute lung injury. The special arrangement with the University of Minnesota, Minneapolis, is essential to characterize some of the translation initiation proteins to be used in Aim 1 (eIF4E wild-type mutants, 4E-BP1 wild type and mutants) and to maintain the 4E-BP1 knockout mice to be used in phase II of the project. The Canadian scientist will maintain and characterize the knockout mouse colony, preparing and shipping mice for experiments on a regular basis and carrying out the cell-free translation and binding assays on new translation initiation constructs.

A grant was also awarded during FY 98 to the Montreal Heart Institute for a joint study of postmenopausal hormone replacement therapy after CABG surgery. The randomized, double-blind, controlled trial is testing the hypothesis that postmenopausal hormone replacement therapy in women after CABG surgery will reduce the occurrence of graft occlusion and delay the development of graft atherosclerosis. The primary outcome variables will be the occurrence of graft occlusion at 6 months and the change in severity and extent of atherosclerosis in saphenous vein grafts over 3 years.

China

Formal scientific exchanges between NHLBI and China began in 1981 and continue through to the current U.S.-China Agreement in Health, signed in October 1998. Joint protocols were developed for epidemiologic studies in China that could be linked with comparable U.S. studies. The goal was to develop expertise, technology, and personnel for epidemiologic research in China, by using internationally standardized methods to carry out cross-sectional and prospective population studies on CVD and pulmonary disease and their risk factors. To ensure comparability of data on trends and rates of disease, the studies have involved the Collaborative Studies Coordinating Center, University of North Carolina, Chapel Hill, and the Centers for Disease Control and Prevention, Atlanta, Georgia. Many joint research reports based on comparative data generated from this exchange program are being prepared for publication.

The initial joint studies in 1983–1985 included more than 10,000 men and women divided into four groups (Beijing and Guangzhou, urban and rural). All four groups have had follow-up for deaths, disease events, and trends in risk factors. Data have been collected over many years to determine the development of hypertension, acute myocardial infarction, and stroke, and the occurrence of sudden death in the study participants. The results show that, with new trends in socioeconomic development and new patterns of disease, prevention of CVD and pulmonary disease is an urgent public health task in China.

A joint working meeting was held in Shanghai, in May 1998, to review the progress made on laboratory tests that provide crucial data for the joint epidemiologic studies. Plans for continuation of the studies were also made, particularly focusing on recommendations for the fourth survey, scheduled to begin in the fall of 1998. The objectives of this survey are to (1) measure the current level of major cardiovascular and cardiopulmonary risk factors among the four Chinese populations being studied in North and South China; (2) compare current levels of major risk factors among these populations; (3) measure changes in major risk factors in comparison to baseline; and (4) explore associations between the change in socioeconomic status and trends of CVD risk factors. Issues concerning measures to ensure comparability of data to be gathered in the fourth survey with data from previous surveys were discussed, as well as measures to prevent problems with data analysis. Lists were developed of supplies and spare parts for laboratory equipment to be used in testing the participants in the Chinese study. The U.S. side has provided the necessary laboratory supplies for implementing the survey.

Czech Republic

Scientific cooperation between the United States and the Czech Republic is conducted under the Agreement on Cooperation in Culture, Education, Science, and Technology, signed in Prague, in April 1986. In 1988, a Summary of Discussion for Cooperation in Cardiovascular Research was signed by the Director, NHLBI, and the Director of the Institute for Clinical and Experimental Medicine (IKEM), to establish a program of scientific exchanges and technology sharing. In August 1990, the new Minister of Health of the Czech and Slovak Federal Republic reaffirmed interest in continued cooperation with NHLBI in cardiovascular research. The two republics of Czechoslovakia split on January 1, 1993, and NHLBI continued collaborations with IKEM, in the Czech Republic.

During FY 98, NHLBI continued to support collaboration between scientists from the U.S. Bypass Angioplasty Revascularization Investigation (BARI) and a parallel clinical research study in Prague. The BARI project compares the long-term safety and effectiveness of percutaneous transluminal coronary angioplasty (PTCA) with coronary artery bypass surgery as a first treatment strategy for advanced ischemic heart disease. This collaboration continues to provide U.S. specialists with new insights that could not be gained from the U.S. patient population alone, while giving Czech physicians an opportunity to attain a level of expertise and to study cases comparable with those in the U.S. BARI centers. As a result of this collaboration, the Czech Republic has become one of the most advanced Eastern European countries in technologies of coronary revascularization. Czech invasive cardiology laboratories are now as well equipped as those in the United States.

U.S. investigators have benefited from this collaboration, which has provided important information on patients in different age groups and disease profiles. At baseline, the Czech patients were generally 10 years younger than U.S. patients (52 vs. 62 years old); were symptomatically more stable, with higher levels of cholesterol (263 vs. 214 mg/dL) and higher smoking rates; and had angiographically more severe disease than U.S. patients in the same age group. The collaboration with the Czech study is making a valuable contribution to the understanding and treatment of ischemic heart disease, thereby broadening the generalizability of the U.S. BARI study results.

In addition, NHLBI supports a dynamic 10-year follow-up (through 2002) for evaluation of PTCA and bypass surgical revascularization patients. This study is proceeding under a cooperative agreement among the University of Pittsburgh (Pennsylvania) BARI registry center; IKEM, supported by the Czech government; and NHLBI. The inclusion of the Czech clinical study in this follow-up evaluation attests to the level of expertise achieved from the U.S.-Czech collaboration. IKEM is one of 16 registry clinical sites studying the patients in the BARI study. The U.S. and Czech scientists will compare results and data from the beginning of the study, as well as the evolution and application of new catheter-based technologies and other revascularization techniques.

Egypt

Egypt has one of the highest rates of hypertension in the world. About one in four adults has elevated blood pressure and is at risk for complications such as heart disease, stroke, and kidney failure. The economic impact of hypertension in Egypt can be measured in billions of dollars per year. There is great concern about the future health of the Egyptian population and the need for hypertension prevention and control.

These conclusions were based on a comprehensive project for the prevention and control of hypertension in Egypt that was developed by U.S. and Egyptian scientists in 1991. The purpose of the project was to study the prevalence of hypertension among Egyptians, characterize the influence of environmental and behavioral factors, determine familial and racial influences, and study the cardiac changes associated with hypertension. The project further aimed to bring the latest information and technology to bear on the problem.

Randomly selected Egyptians in different regions were screened during household visits in the first phase of the study. In the second phase, all patients with hypertension and matched control subjects underwent an extensive medical evaluation to identify complications of hypertension and to explore potential determinants of hypertension and its complications. Data were presented at international meetings, and research reports were prepared for publication. A Pan Arab Conference on Hypertension was held in Egypt, in December 1993, as a direct outgrowth of the U.S.-Egypt collaboration. This meeting was followed by the second joint conference in Lebanon in 1995, and the third joint conference is planned in the United Arab Emirates in 2000.

As a result of the U.S.-Egypt collaboration, a library, information network, and laboratories have been established at the Hypertension Reference Center, Cairo, for physicians and scientists for consultation and study. In addition, the Egyptian team established an Egyptian Hypertension League, and Egypt has joined the World Hypertension League as a member. A self-sustaining research and education program in Egypt has also been planned. Formal collaboration between the United States and Egypt on phase I of this program was terminated in March 1994 with a final joint meeting in Egypt, after completion of the survey. Informal collaboration between U.S. and Egyptian scientists and joint publications of the results continue.

In FY 97, an Egyptian scientist visited the Cleveland Clinic, Ohio, for 1 month, to study the short-term in-hospital outcome after stenting in patients with threatened or established vascular closure after PTCA. NHLBI has agreed to receive two additional Egyptian scientists for joint research with U.S. scientists in the field of cardiopulmonary research and disease prevention.

A proposal for continued collaboration in hypertension prevention and control is under consideration by Egypt and the United States.

Georgia

Asthma and hypertension were identified as the areas of highest priority for cooperative activities, in a Summary of Discussion signed during a visit to NHLBI by the Deputy Minister of Health of Georgia, in February–March 1996. These plans grew out of exchanges in the area of asthma management initiated in FY 95 with the Department of Allergology, State Medical University, Tbilisi. Previously, U.S. and Georgian scientists from the Research Institute of Experimental and Clinical Therapy, Tbilisi, had research activities in the areas of hypertension and immunogenetic studies of cardiomyopathy.

The Deputy Minister of Health has been appointed as a member of the Advisory Board for the NHLBI-WHO Global Initiative for Asthma (GINA) project. NHLBI has worked with Georgian scientists on the translation and printing of all the GINA documents into the Georgian language. These printed materials will now be widely distributed by the Ministry of Health. Plans have been developed for the visit of a three-member working group to Georgia in FY 99. Future directions on all aspects of research on asthma will be actively pursued.

Germany

The United States and Germany are cooperating in biomedical research under an agreement signed in 1976 and renewed periodically since then. The cooperation encompasses research on CVD and pulmonary disease and involves basic and applied research.

Staff from NHLBI and U.S. and German researchers met in FY 96 to begin mapping the rat genome, make plans to reduce duplicative efforts, create cross-referenced reagents, and produce interdigitated maps. This mutual interest was expressed contemporaneously with the National Institutes of Health (NIH) Rat Genome project and the European Rat Genome project. Scientists from these projects met for a U.S.-German joint workshop in Toronto, in March 1997. They discussed the progress and status of studies of human subjects, the development of rat models, genetic mapping, cDNA (complementary DNA) libraries, bioinformatics and communications and shared technologies, and radiation hybrid panels. The coordination of centers and scientists from the United States and Germany continued during FY 98 as a major focus for effective collaboration in genetic research. Researchers in both countries are planning to present major progress reports and findings at a joint workshop to be held in the spring or summer of 1999.

Pulmonary research became a part of the NHLBI-German cooperation in 1984, starting with a joint meeting in Heidelberg, in November of that year, on Basic and Clinical Research on Pulmonary Fibrosis. As a result, a long-standing fruitful collaboration was implemented between the Harvard School of Public Health, Boston, Massachusetts, and the Institute for Inhalation Biology, Phillips University, Marburg. To date, researchers from these organizations have produced more than 20 joint publications and 11 joint abstracts, providing a valuable source of information for future program direction. Their work has focused on the use of inert monodispersed aerosols to detect and diagnose pulmonary disease; anatomic distribution of particles deposited in the lungs from inspired aerosol boluses; the mechanisms by which alveolar lung macrophages clear deposited particles; and the effects of sulfite ions on cells and tissues in the lungs. This collaboration has resulted in the development of important new diagnostic tests to supplement routine pulmonary function tests and longitudinal studies.

The most recent U.S.-German workshop was held on Asthma in Early Childhood, in Berlin, in June 1998. Pulmonary researchers from the United States and Germany reported the latest information on the epidemiology of asthma, genetic markers, cellular mechanisms of airway hyperreactivity, asthma and infection, and primary and secondary prevention of bronchial asthma. This meeting provided both sides with an opportunity to share the results of timely research topics, develop new alliances, and plan new directions for future joint research.

Also, during FY 98, researchers from the Justus Liebig University, Giessen, collaborated with scientists from the Allergy and Clinical Immunology Division, Francis Scott Key Medical Center, Johns Hopkins Asthma and Allergy Center, Baltimore, Maryland, in studies of innervation of the airways and the effects of allergic inflammation on neurochemical and electrophysiological phenotypes of airway sensory nerves. Since 1994, five joint papers have been published and four additional manuscripts have been submitted for publication as a direct result of this collaboration, identifying the specific origin of nerve fibers regulating bronchodilation of airway smooth muscle and further characterizing the phenotypes of these important autonomic nerves. In addition, the scientists have combined physiological and morphological data relating to heme oxygenase, a novel regulatory enzyme in autonomic nerves that generates biologically active carbon monoxide from heme proteins.

Hungary

Scientific cooperation between the United States and Hungary was initiated in 1981, following a government-to-government Agreement on Culture, Science, Education, and Technology, signed in April 1977. Bilateral exchanges of scientists and technologies have been carried out since 1982, under a continuing agreement between NHLBI and the Hungarian Institute of Cardiology.

In October 1994, the Parliamentary Secretary of State, Ministry of Welfare of Hungary, visited NHLBI with the Hungarian Science Attaché, to confirm Ministry interests to collaborate in joint research. He stressed that coronary heart disease is the number one cause of death in Hungary. Hungarian national health policies are placing increased emphasis on primary and secondary prevention and on nonpharmacological and pharmacological treatment of hyperlipidemias and hypertension.

U.S. and Hungarian coordinators saw an opportunity for collaboration during March–May 1998. The Head of the Cardiomyopathy Clinic and an associate professor of cardiac surgery from the Hungarian Institute of Cardiology worked with U.S. scientists at the University of Pittsburgh, Pennsylvania, on new medical treatments of chronic congestive and refractory heart failure; noninvasive methods for evaluation of patients with chronic heart failure; and use of β-blocker therapy. The Hungarian researchers provided specialized expertise on noninvasive assessment of cardiac function and on patient selection and study design for investigation of the role of β-blockers in therapy for congestive heart failure.

In September 1998, the Associate Director for International Programs and the International Program Officer for Hungary, NHLBI, met with the Science and Technology Attaché at the Embassy of Hungary, to discuss coordination of new opportunities for exchanges of scientists in cardiovascular research. A follow-up meeting is planned to discuss specific ideas for joint projects during FY 99.

India

NHLBI has collaborated with scientists in India for more than 20 years. Currently, U.S. and Indian researchers collaborate under the terms of the Gandhi-Reagan Science and Technology Initiative. Joint projects are reviewed for support by the Indo-U.S. Science and Technology Subcommission. In addition, in-country support is provided by NHLBI under this umbrella initiative.

There is ongoing collaboration between an NHLBI Nobel Laureate who is Chief of the Laboratory of Biochemistry and Genetics and an emeritus scientist in the Department of Biochemistry, All India Institutes of Medical Sciences, New Delhi. The project deals with two grants: one newly awarded in FY 98 and another nearing completion. Both grants deal with aspects of the development and differentiation of the nervous system, by using the latest molecular biology techniques to study growth factors in conditioned C6 glioma media and their implications in viral diseases of the central nervous system. Several new discoveries have been made in this collaboration, leading to a series of publications, including a report on An IL-6–Mediated Growth Loop in the Human Glioblastoma Multiforme Cell Line U87MG and a report on Monoclonal Antibodies Against Human Glioblastoma Multiforme (U87MG). Two other manuscripts, one on A Device for Transplantation of Single Cells and another on A Device for Single-Cell Transplantation With Minimal Transfer of Suspension Fluid, deal with a new technology for transplanting single identified cells into specific regions of the brain with a high degree of precision. The Indian investigator is using this device to microinject cells into neonatal and adult brains and evaluate the state of transplanted cells by species-specific monoclonal antibodies.

The joint project has reported the generation of a monoclonal antibody, 6DS1, against a human glioblastoma multiforme cell line that recognizes the 38-kilodalton cell-surface antigen on glial tumors. The scientists also have purified the antigen protein from the glioblastoma multiforme cell line U87MG and have used it to produce hybridomas secreting monoclonal antibodies that may recognize specific epitopes on this protein. They anticipate that this research could lead to the development of a diagnostic tool in the histopathological grading and localization of human brain tumors.

The newly awarded grant, including the Chief of the Laboratory of Biochemical Genetics as co–principal investigator, focuses on the immortalization of human fetal neurons, the role of trophic factors in their survival, and the study of apoptopic features of selective neuronal death during aging of neurons in culture. The goals of this project are to culture and immortalize human neuronal cell lines and introduce these cells into the rodent central nervous system to assess their differentiation potential. The grant was awarded in January 1998 for 5 years. The Indian scientist is planning an exchange visit to NHLBI during FY 99.

Italy

NHLBI's cooperation with Italy is conducted under the 5th U.S.-Italy Science and Technology Agreement, which was signed in Washington, D.C., on November 5, 1997, and a joint statement on international cooperation, entitled A New Partnership for a New Century, which was signed on May 6, 1998, by President Bill Clinton and Prime Minister Romano Prodi. Under these agreements, NHLBI and the Institute of Pharmacology, University of Milan, are collaborating in cardiovascular research of mutual interest and benefit. Since the 1st U.S.-Italy Joint Workshop on Measurement and Control of Cardiovascular Risk Factors was held in Rome, in December 1978, between NHLBI and the University of Milan, scientists from both sides have conducted many joint research projects and shared information on a range of topics. Joint symposia have given U.S. and Italian scientists the opportunity to share recent data, develop proposals for new research projects, and discuss new research priorities.

A U.S.-Italy workshop in the pulmonary area was held in Ferrara, in October 1997. It focused on Noninvasive Assessment of Airway Inflammation. Investigators from both countries shared technologies in the following areas: inflammation in chronic obstructive airway disease; distribution and chronobiology of inflammation; methods and validation of sputum induction and content; circulating markers of airway inflammation; the role of nitric oxide (NO); the differences in airway diseases and disease severity; induction of sputum to monitor airway inflammation in clinical trials; and the effects of long-acting bronchodilators on sputum cells and mediators.

The next U.S.-Italy joint symposium in the pulmonary area will address Biochemical Markers and Assessment of Lung Diseases: Prognostic, Diagnostic, and Therapeutic Implications. The meeting will be held in Palermo, on October 14–15, 1999.

The most recent U.S.-Italy joint symposium in the cardiovascular area was held in Bethesda, Maryland, in November 1998. The topic was Vascular Biology of Atherosclerosis. The following areas were discussed: pharmacological control of protein prenylation and the effect on arterial smooth muscle cell proliferation; mechanisms and consequences of endothelial cell apoptosis; triggers and modulators of early atherogenesis; homocystine, oxidative stress, and atherosclerosis; the monocyte and macrophage link between atherosclerosis and thrombosis; molecular genetics of the vessel wall (e.g., vascular smooth muscle cell regulation); immune responses of the arterial wall including scavenger receptors; cytokine activation of endothelial cells; and future therapeutic targets for the treatment of dyslipoproteinemias.

As a result of this meeting, the scientists have proposed the following topics for future collaboration: new technologies in vascular biology, atherosclerosis, and atherothrombosis; the role of inflammation and infection in CVD; novel approaches to gene therapy; regulation and control of vascular growth; and functional genomics in CVD. The next U.S.-Italy symposium on cardiovascular research will be held in Venice, in October 1999.

U.S. and Italian scientists continued to collaborate on a joint project on vasoconstriction in the liver. This project is a collaboration between New York Medical College, Valhalla, and the Institute for Clinical and Experimental Medicine, Padua. It focuses on impairment of renal function in patients with cirrhosis; vasoconstrictors produced in the liver or introduced by portal inflow; and the pathogenesis of hepatic portal hypertension. The scientists have developed new pharmacological approaches to this clinical problem. These experiments have been carried out in isolated perfused rat liver. The investigators have verified the role of cytochrome P-450–dependent metabolites of arachidonic acid, 20-HETE, and 11,12-EET in the control of portohepatic resistance and response to endothelin-1 and have evaluated their level of inhibition on basal portal pressure and on vasoconstriction by endothelin-1.

Another collaborative study on CVD relates to cholesterol transport. A scientist from the Institute of Pharmacological Sciences, University of Milan, worked with the chairman of the Department of Pathology, University of Washington, Seattle, on a project that provided evidence for the role of prenylated proteins in the emergence of cells from the quiescent state to cell-cycle progression. The studies focused on Rho A and B, geranylgeranylated protein products of a gene inducible by platelet-derived growth factor and other factors. The Rho A protein regulates the assembly of focal adhesions and the organization of the actin cytoskeleton. The role of Rho B is still unknown. The scientists plan to continue efforts to determine whether Rho B is a key regulator of cytoskeletal integrity, cell morphology, adhesion, and migration.

Also during FY 98, a scientist from the Department of Preclinical and Clinical Pharmacology, University of Florence, continued to work with a professor of medicine in the Division of Hypertension and Endocrinology, Case Western Reserve University, Cleveland, Ohio, to elucidate signaling pathways in angiogenesis and vascular remodeling. The Italian side contributed a coronary endothelial cell line that is difficult to obtain in the United States. The scientists carried out studies of mitogen-activating protein kinases and c-jun *N*-terminal kinase in epithelial cell lines from kidney proximal tubules of hypertensive (SHR) and normotensive (WKY) rats and in coronary venular endothelial cells.

In the pulmonary area, joint research continued among professors of pharmacology at the University of Florence and the University of Milan and a professor of medicine and physiology at CVRI, University of California, San Francisco, on the effect of endogenous NO on bronchoconstriction induced by cold air inhalation in guinea pigs and mediated by kinins and tachykinins. The researchers also studied the role of NK_1 receptors in neutrophil–epithelial interactions and reported that interleukin 8 (IL-8) injected into the airway lumen of the guinea pig trachea caused neutrophil recruitment. The U.S. researcher had previously shown that neutrophil elastase is the most potent secretagogue of goblet cells involved in peripheral airway obstruction by mucous plugs in critically ill patients with asthma. These studies were followed by a collaborative study in patients with asthma, which showed that NO also participates in asthmatic bronchomotor responses in human disease. Future collaboration will focus on the role of tachykinins, epithelial cells, and macrophages in the release of IL-8 and on the consequent accumulation of neutrophils in the lungs and airways.

Japan

For more than 20 years, U.S. and Japanese scientists have collaborated in cardiovascular research, providing unique opportunities for comparative studies and new insights into the causes of CVD. For instance, the patterns of CVD vary greatly between the United States and Japan, particularly with regard to stroke and coronary heart disease. This observation has led to comparative studies focusing on four areas: (1) dietary studies of the positive or negative effects of calcium, potassium, physical exercise, and alcohol on hypertension; (2) studies of the progression of hypertension in children, as a predictor of high blood pressure in adults; (3) pathology of intracerebral arteriosclerosis; and (4) community-based intervention of dietary and other risk factors.

NHLBI's current cooperation with Japanese scientists is based on a U.S.-Japan Agreement on Cooperation in Research and Development in Science and Technology, signed in June 1988 and renewed in June 1993. Periodic Summaries of Discussion outlining specific collaborative activities in basic research, epidemiology, and community studies have been signed by the Director, NHLBI, and the President of the National Cardiovascular Center Research Institute. The most recent document was signed in April 1998 at the conclusion of a joint U.S.-Japan symposium in Nara. At that meeting, scientists reported the results of ongoing joint research, as well as new findings in genetic epidemiology.

The delegates to the U.S.-Japan symposium reported further increases in the prevalence of CVD risk factors in Japanese populations, as diets have become more westernized. Also, there are marked differences in CVD patterns in the United States and Japan. The prevalence of hypercholesterolemia has increased in Japan during the past 10 years. The incidence rate of stroke in Japan continues to be higher than that of acute myocardial infarction. The age-adjusted annual incidence of first-ever stroke in 1997 was 99 in men and 58 in women per 100,000 population, whereas the incidence of acute myocardial infarction was 15 and 26 per 100,000 population, respectively. U.S. delegates reported on population trends in the prevalence and incidence of CVD in the United States; effective strategies for risk reduction of atherosclerosis; genetic epidemiology of CVD risk factors; and use of whole-genome screens to find new genes for atherosclerosis susceptibility. Participants also discussed the economic and epidemiologic impact of hypertension and its treatment, as well as advances in health economics.

At the conclusion of the 1998 symposium, both sides proposed to continue joint studies in the four major areas:

- prevention of hypertension through diet and other nonpharmacological approaches;
- blood pressure and other CVD risk factors among children and young adults;
- comparative pathology of atherosclerotic and hypertension lesions; and
- programs for community intervention and prevention of CVD.

During FY 98, the principal investigator for the U.S. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study at Louisiana State University Medical Center, New Orleans, visited the laboratories of a number of collaborators in Japan, including a cardiovascular pathologist working in a parallel PDAY study at the National Cardiovascular Center, Osaka. He also met with a researcher at Toho University, Tokyo, about publication of immunohistochemical findings on apolipoproteins in the arteries of PDAY subjects. Other visits involved collaborators at Keio University, Hirosaki, and Kugayama Hospital, Tokyo, on the investigation of peroxidability of lipoproteins and the effects on atherosclerosis. The visit also included scientific discussions at the Department of Medicine, Shimane University, Izumo, regarding participants in the Honolulu Heart Project and the Ten Cities Study in Japan.

Korea

NHLBI cooperates with the Korean Advanced Institute of Science and Technology (KAIST) under the U.S.-Korea Science and Technology Agreement, originally signed in 1976. The joint collaboration has focused on the role of oxygen radical–mediated oxidation of proteins and lipids in various biological processes, including aging, atherosclerosis, ischemia–perfusion injury, and inflammation and signal transduction.

In 1992, the Laboratory of Biochemistry initiated a collaboration with the Research Center for Molecular Microbiology (RCMM), Seoul National University. In 1995, this collaboration was renewed and expanded in a signing ceremony between the Director, NHLBI, and the Director, RCMM. During FY 96, the Director, NHLBI, made a reciprocal visit to RCMM and presented a lecture on Future Direction in Cardiovascular Research.

During FY 98, Korean scientists from Seoul National University continued to share technologies and expertise with the Laboratory of Biochemistry, NHLBI. A researcher from the Department of Microbiology collaborated on studies of free radicals and oxidative stress in the signal transduction pathway, with a focus on the correlation between NF-kB activation and the generation of intracellular free radicals, using electron paramagnetic resonance spectroscopy. The scientists studied the structure and reactivity of cross-linked proteins formed as glycated end products, which accumulate with atherosclerosis, diabetes mellitus, and aging. These advanced glycated end products are associated particularly with long-lived proteins, such as collagens, lens crystallins, and nerve proteins. Some of these results have been published in the *Journal of Biological Chemistry.* Other collaborative work includes studies of the activation mechanism of the human manganese superoxide dismutase gene, which is mediated by oxidative stress. These joint research projects will continue in FY 99.

Also, since 1990, the Laboratory of Biochemistry, Chonnam National University, Kwangju, and Bai Jai University, Dae-Jon, have collaborated on studies of protein damage incurred by mixed-function oxidation systems of importance in the study of cell death. The outcomes of this research have applications for many areas of medicine and further scientific study. The Laboratory of Cell Signaling is carrying out this collaborative program with the Korean Research Institute of Bioscience and Biotechnology (KRIBB), KAIST, Seoul.

Another collaboration between KRIBB and the Laboratory of Cell Signaling, NHLBI, focused on the structural characterization of thioredoxin peroxidase, an antioxidant of H_2O_2. Although peroxidase is considered to be a toxic byproduct of respiration, increasing evidence suggests that the production of H_2O_2 may be an integral component of membrane receptor signaling. The researchers also studied the second-messenger function of H_2O_2 and the identification of the cellular target molecules on which H_2O_2 acts. The Chief, Laboratory of Cell Signaling, visited KRIBB during FY 98 to collaborate on a joint research report dealing with the determination of one of three peroxiredoxin genes characterized to date and to initiate joint research on another gene. This collaboration also focuses on the role of NO generated by cytokines in lymphocytes and on proteins regulated by NO. The scientists plan joint research on cell thioredoxin peroxidase peroxiredoxin knockout mice, which are being developed for use in these studies.

Kyrgyzstan

U.S.-Kyrgyzstan collaboration in pulmonary research, which began as an extension of activities initiated under the U.S.-USSR exchange agreement, has continued to yield joint publications reporting on research results. During FY 98, an article on the results of basic research experiments showed that unique phenotypes and distinct growth capabilities were exhibited in smooth muscle cells isolated from mature vascular media. This article was published in December 1997 in Circulation Research.

Pakistan

An agreement between NHLBI and the National Institute of Cardiovascular Diseases, Karachi, provides the framework for a joint epidemiology study initiated in 1993, with the goal of increasing knowledge and awareness of CVD, its determinants, and effective efforts to prevent it. The joint study also aims to expand the Pakistani capacity for assessment and modification of CVD risk factors. One of the questions being explored is whether CVD prevention programs in the United States can be adapted to Pakistani subpopulations, to reduce high rates of morbidity and mortality.

The study participants are from intervention families and control families, and their progress is being compared. Data analysis will assess the short-term effectiveness of the intervention. The partnership of both Institutes is evident in the design, planning, data standardization, control, and analysis. Exchanges of scientists, joint meetings, and development of joint research publications are also included within the scope of the project. During FY 98, a no-cost extension of the project was arranged through May 1999. The visit of a Pakistani scientist to the United States is planned for FY 99, to evaluate progress and define further plans for continuing the joint study.

Poland

The U.S.-Poland collaboration in research on CVD was first conducted under the U.S.-Poland Agreement for Health Cooperation, signed by the U.S. Secretary of State, Henry Kissinger, and the Deputy Prime Minister and Chairman of the Planning Commission of the Polish People's Republic, Mieczyslav Jaqielski, on October 8, 1974. Collaborative interests in cardiopulmonary research have been outlined in Summaries of Discussions between NHLBI and the Polish National Institute of Cardiology. The most recent document was signed in September 1998.

.Collaborative research between the United States and Poland is of special interest in view of the marked differences in trends for CVD and risk factors in the two countries. Although the magnitude of the disability from ischemic heart disease was high in both countries between the years 1974 and 1994, death rates have declined by 43 percent in the United States, while they have increased by approximately 70 percent in Poland. For COPD, mortality rates declined slightly in the United States for men and significantly in Poland for men and women, during 1980 to 1993. The United States experienced a significant increase in these rates for women during the same period (World Health Statistics Annual, WHO). These differences in trends have provided a focus for joint research to better understand the etiology of cardiopulmonary disease and its risk factors.

Since 1980, the Collaborative Studies Coordinating Center, Chapel Hill, North Carolina, has carried out joint analyses to compare epidemiologic data from the Pol-MONICA Study with data from the U.S. Lipid Research Clinics Program Prevalence Study (U.S.-Poland Collaborative Study) and the U.S. Atherosclerosis Risk in Communities (ARIC) study. In these joint efforts, scientists in Warsaw, Kraków, and the United States have assessed the prevalence of cardiopulmonary diseases and their risk factors in urban and rural populations and the between-country differences in trends in prevalence and risk factors.

Exchanges of scientists continued during FY 98. A researcher from the Department of Medicine, Jagellonian University, Kraków, worked with the Director of the Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital, Boston, Massachusetts, in September–November 1998. The U.S. researcher has been working on unique biosynthetic actions in the asthmatic lung, which are triggered by aspirin. This work involves aspirin acetylation of COX-2 in airway epithelial cells or vascular endothelial cells, to generate a novel series of eicosanoids termed 15 epi-lipoxin A_4 or aspirin-triggered lipoxins. The Polish investigators provided samples from their patient population with aspirin-triggered asthma. The presence of 15 epi-lipoxin A_4 in these samples was measured.

A U.S.-Poland Joint Workshop in Cardiopulmonary Disease was held in Chapel Hill, North Carolina, in March 1998. This workshop provided an opportunity for researchers from both countries to discuss a number of research reports resulting from analyses of data from collaborative studies. The following topics were addressed: environmental, dietetic, gender, and genetic risk factors for cardiopulmonary disease in U.S. and Polish populations; blood pressure distributions in both populations; and smoking trends. A presentation on the latest findings and directions for future research was given by the Director, National Center on Sleep Disorders Research. The March workshop celebrated 20 years of collaboration between U.S. and Polish scientists. A 20-year scientific report and a 20-year history are being developed, to summarize the joint accomplishments of the U.S.-Poland collaboration in cardiopulmonary research.

A U.S.-Poland working meeting in cardiovascular epidemiology was held at the National Institute of Cardiovascular Disease, Warsaw, in October 1998.

Russia

NHLBI's collaboration with Russia and the former Soviet Union has been ongoing for more than 25 years under a series of agreements. The current agreement, signed in January 1994 in the area of public health, included collaboration in eight scientific areas of CVD and pulmonary disease.

NHLBI, along with four other NIH Institutes (National Cancer Institute, National Institute on Drug Abuse, National Institute on Alcohol Abuse and Alcoholism, and National Institute of Dental Research), has also been an active participant in the Gore-Chernomyrdin subcommittee meetings in the priority area of health promotion and disease prevention. Exchanges of information with Russian colleagues have been ongoing (1) to discuss potential collaborative projects that may build on previously successful research projects and (2) to establish new and alternative mechanisms for funding joint research.

During a meeting in February 1998 between the coordinators of the U.S.-Russian collaboration in cardiopulmonary research—the Director of NHLBI, the Director of the Cardiology Research Center of Russia, and the Director of the National Center for Preventive Medicine, Moscow—an agreement was reached to restructure the collaboration into two main areas: CVD and pulmonary disease. Both sides agreed on joint plans, including a workshop to be held in the United States, in 1999, on Vascular Biology in the Heart and Lungs. Another workshop will be held in Russia on the topic of arrhythmia. The priority areas agreed on for CVD include basic research; prevention, education, and control in heart disease; hypertension; continued joint epidemiologic studies; and management of ischemic heart disease. In the area of pulmonary disease, the priority areas are basic research, genetic studies, prevention, asthma, and pulmonary hypertension. Exchanges of scientists in the cardiovascular and pulmonary areas will also be continued.

During FY 98, joint research continued in the area of vascular biology and hypertension. Vascular biology is an area of strong interest, focusing on multidisciplinary approaches to the examination of cell behavior, including analysis of the cell cycle in response to hypertension and atherosclerosis. During October 1997–February 1998, a scientist from the Cardiology Research Center, Moscow, worked in the Division of Intramural Research, NHLBI, to continue joint research on regulation of the molecular mechanisms of smooth muscle contraction. Publication of results is anticipated.

South Africa

The 2nd U.S.-South African Workshop on Hypertension in Blacks was held at the NIH in Bethesda, Maryland, on July 16–17, 1998. Key U.S. and South African investigators had an opportunity to review the latest research on hypertension and CVD prevention and to develop collaborative plans for conducting joint studies to increase understanding of hypertension in the black population in each country. Both the United States and South Africa recognize the importance of providing scientists from each nation with opportunities to discuss potential initiatives with their counterparts.

The participants concluded that scientific exchange activities in several priority areas related to the primary prevention of hypertension would benefit both nations. They agreed on continued collaborative activities, including exchanges of scientists and information during the next 2 years in the following areas identified as high priority: (1) joint studies on salt sensitivity, body mass index, and hypertension; (2) hypertension in pregnancy; (3) community studies of hypertension prevention and intervention; and (4) exchanges between deans of U.S. and South African Schools of Public Health.

The workshop follows up previous exchange activities that have been under way during the past several years, especially since the 1st Joint U.S.-South Africa Workshop on Hypertension in Blacks, in Cape Town, in December 1996. Formal and informal meetings between NHLBI and South African scientists and officials have been held periodically to develop joint planning efforts to better address the serious health problem of CVD in blacks in the United States and South Africa.

Uganda

Joint research in Uganda focuses on preventing transmission of acquired immunodeficiency syndrome (AIDS) from mothers to infants. A study funded by NHLBI and the National Institute of Allergy and Infectious Diseases is exploring the use of immunoglobulin to prevent vertical transmission of the human immunodeficiency virus (HIV) from mothers to infants. This double-blind study began in 1993 and continued for 5 years. The collaborating parties included Case Western Reserve University, Cleveland, Ohio; Makerere University; the National Bacteriologic Laboratory of Sweden; and the Ugandan Ministry of Health.

Vietnam

Both the United States and Vietnam recognize the importance of research on blood diseases, particularly hepatitis and aplastic anemia, which are serious health problems in both countries. The safety of the blood supply is also an important concern for patients requiring blood transfusions and for their physicians. Officials and scientists agree that more rapid progress could be made by joining forces and working collaboratively against these serious health threats. Joint research in the area of blood diseases has been under way with Vietnam since 1993, as an extension of the 10-year U.S.-Thai cooperation.

In the fall of 1997, a Vietnamese scientist visited the Bone Marrow Transplantation Unit, NHLBI, for 2 months of joint research on bone marrow transplantation. The investigator developed protocols for bone marrow transplantation in Vietnam and compared graft-versus-host disease rates in U.S. and Vietnamese populations.

In the spring of 1998, two U.S. extramural scientists and the Head, Hematology Branch, NHLBI, visited Vietnam to present another in a series of annual seminars in Ho Chi Minh City, to Vietnamese scientists and health care professionals. The seminar focused on the practice of transfusion medicine and was held in conjunction with the National Hematology meetings of Vietnam. Lectures were presented on aplastic anemia; paroxysmal nocturnal hemoglobinuria; viral infections and their effect on the blood supply; virus detection methods; diagnosis of hemolytic anemias; blood transfusion practices; and potential alternatives to red blood cell transfusion. The scientists met with investigators at the National Institute of Hematology and Blood Transfusion, Hanoi, and Bach Mai Hospital, Hanoi University Medical School.

Collaborative interests were further strengthened during the visit, when the Director, National Institute of Hematology and Blood Transfusion, Hanoi, agreed to collaborate on the collection of valuable serum and stool specimens from patients with seronegative acute hepatitis, which is reported to be particularly common in Vietnam. U.S. investigators will use these specimens for molecular studies, in efforts to discover a new virus responsible for this type of acute hepatitis, fulminant hepatitis of childhood, and posthepatitis aplastic anemia. Specimens of liver and bone marrow from patients with these conditions have not proved useful in experiments, probably because of severe damage to the liver and bone marrow, due to the late stage of disease. Scientists in both countries are looking forward to continued collaboration.

Activities With International and Multinational Organizations

The global health threats of heart, lung, and blood diseases continued to be the focus of NHLBI's activities with international agencies and multinational organizations during FY 98. NHLBI staff serve as consultants to WHO, PAHO, and other international organizations that contribute to worldwide plans for the prevention and control of CVD and pulmonary and blood diseases in both developed and developing countries. During FY 98, new collaborations with PAHO in CVD research were developed in conjunction with the joint celebration of the 50-year anniversaries of NHLBI and WHO. Since 1980, the Institute has served as a WHO Collaborating Center for Cardiovascular Research and Training for the Americas and, in this role, provides information and data for use throughout the world. The center provides advisory services to WHO, assists in the training of WHO fellows, and provides advice on the collection and exchange of information and data on activities in the field of CVD research, especially prevention and control of CVD and advances in basic research.

The NHLBI Director and senior staff participate in WHO advisory committee meetings and contribute to WHO reports in a number of areas. The Director also serves as special advisor to the World Hypertension League Board. The Coordinator of the Institute's National High Blood Pressure Education Program is the North American editor of the World Hypertension League Newsletter.

NHLBI, the Mexico Cardiovascular Institute, and the Mexican Program in Epidemiology are developing plans to exchange scientific information on the public health burden of hypertension and the role of primary prevention of hypertension. NHLBI also collaborates with the WHO Division of Noncommunicable Diseases on its study of Integrated Programs for Community Health in Noncommunicable Diseases and has developed contacts for CVD control with the WHO Western Pacific Regional Office.

NHLBI is collaborating with representatives from other G7 countries in developing a global database in CVD and standardized approaches to using electrocardiograms in diagnosis and classification of patients with myocardial infarction and congestive heart failure. On behalf of the United States, NHLBI has the opportunity to share data on randomized control trials, epidemiology studies, and registries, as well as documents such as the Adult Treatment Panel II report developed by the U.S. National Cholesterol Education Program and the 6th Joint National Committee report developed by the U.S. National High Blood Pressure Education Program. In return, the United States will gain new knowledge from databases provided by foreign counterparts, such as Germany, Italy, and the United Kingdom.

NHLBI supports two important resources used in nutrition research in the United States and other countries. The first resource is the University of Minnesota Nutrient Data System (NDS), an automated dietary interview methodology linked to data on the content of 92 nutrients in 16,000 brand-name food items. The NDS system is in use, either directly or in modified versions, in several NHLBI international collaborative studies, including studies of cardiopulmonary epidemiology in China and in the Intermap international blood pressure study in China, England, Japan, and the United States. NHLBI also supports the U.S. Department of Agriculture in its efforts to generate analytic data for the U.S. National Food Composition Database. These chemical analysis data are an international research resource, because they represent the world's largest single source of primary information on the nutrient content of foods and are used by many other countries that may not have the resources to establish databases.

NHLBI, WHO, and experts from a number of countries also collaborate on a joint project to address asthma as a serious global health problem. Asthma is estimated to affect more than 150 million people worldwide, and there is evidence that prevalence is on the increase in most countries, especially in children. GINA aims to decrease morbidity and mortality by the development and implementation of an optimal strategy for the management and prevention of asthma. The Global Strategy for Asthma Management and Prevention WHO-NHLBI Workshop Report was published in 1995 and covered information about epidemiology, pathophysiology, management, prevention, risk factors, mechanisms, education, and socioeconomic issues relating to asthma. Three companion documents have been prepared and disseminated through symposia held in each of the six WHO geographic regions. These documents are concise reference materials for patients, as well as physicians and nurses, and include key recommendations to support efforts in designing and delivering effective asthma management and prevention programs in communities around the world. Building on the GINA model, plans are under way to use a similar structure for the development of an international strategy for the diagnosis and management of COPD.

Extramural Programs

International grants, contracts, cooperative agreements, and fellowships with foreign institutions also provide the United States with unique opportunities to draw on worldwide resources and expertise. NHLBI supports a broad range of research projects in heart, lung, and blood diseases, to gain important benefits for national research efforts.

Grants

NHLBI supported 10 foreign investigator projects during FY 98. Six research grants awarded to institutions in Canada included studies of blood–biomaterial interactions; heritage genetics; responses to exercise; risk factors; genes and proteins; genetic risk factors for hyperhomocysteinemia; cardiac lesions in transgenic mice; and activated mutants as probes of receptor functions. Four grants were awarded to institutions in the United Kingdom. These dealt with research on anorectic agents and primary pulmonary hypertension; ontogeny of fetal sensitization to allergens and asthma; human immunovirus monoclonal antibodies; and social and occupational influences on health and illness.

Cooperative Agreements

In FY 98, the University of Manitoba, Winnipeg, collaborated with NHLBI in a study of the efficacy of inhaled corticosteroids in COPD. COPD affects more than 10 million U.S. residents and is increasing in prevalence and as a cause of death. The study is examining the benefits and adverse effects of different intervention approaches. Also, a cooperative agreement for clinical trials was initiated between NHLBI and the University of Manitoba for a long-term follow-up of the international Lung Health Study.

Fellowships

In FY 98, a fellowship and supplement were awarded to a researcher at the University of Cambridge, England, for studies of antithrombin activation and inhibition of proteinase.

International Meetings

NHLBI's Director of the Sleep Disorders Center visited Germany at the invitation of a primary health care group to talk about sleep disorders from a national health perspective. His presentation focused on NHLBI's activities to raise awareness of sleep disorders, among primary care physicians in the United States.

The NHLBI Deputy Clinical Director, Intramural Research, visited Vietnam in March 1998 to conduct a training seminar on blood transfusion medicine. The seminar was held in conjunction with National Hematology meetings of Vietnam.

The Director, Division of Epidemiology and Clinical Applications (DECA), NHLBI, represented the Director, NHLBI, at the 13th

World Congress of Cardiology, in Rio de Janiero, Brazil, in April 1998. The Director, Clinical Applications and Prevention Program, DECA, participated in a meeting of the WHO-International Society of Hypertension Guidelines Committee, in Fukuoka, Japan, on September 29–October 1, 1998. He gave a presentation on dietary sodium and potassium and blood pressure. The Director also participated in the review of successive drafts of the 1998 revision of WHO-International Society of Hypertension Guidelines on the Management of Hypertension. As one of the few meeting participants with direct experience from the 6th Joint National Committee Report, he contributed perspectives from that report.

In May 1998, NHLBI collaborated with PAHO and FIC in the PAHO-WHO-NHLBI-FIC Conference on Global Shifts in Disease Burden. This was the first conference of its kind to feature scientists, researchers, and government officials from across the Western Hemisphere, to address the growing pandemic of CVD in the Americas. The goals of the conference were to use the occasion of the 50th anniversaries of WHO and NHLBI to call attention to the pandemic of CVD in the Western Hemisphere and to seek new ways to prevent and control the spread of CVD in the future.

A staff member from DECA, NHLBI, participated in meetings in Sweden during the summer of 1998. The NHLBI scientist went to Stockholm for joint work with the Department of General and Family Medicine, Karolinska Hospital. The purpose of the visit was to analyze data comparing psychosocial factors and CVD risk in Estonians and Swedes. There has been a significant rise in CVD risk in eastern bloc countries since the breakup of the Soviet Union. This increase cannot be explained by the traditional risk factors. The analysis of these data provides a unique opportunity to increase our knowledge of behavioral factors that may be involved in primary prevention of CVD.

The Coordinator, National High Blood Pressure Education Program, attended the 3rd International Heart Health Conference, in Singapore, on August 29–September 2, 1998. Among the topics discussed were prevention of CVD in developing countries. A policy statement for CVD prevention in developing countries is anticipated.

Intramural Programs and Activities

Scientists from many countries have been given the opportunity to conduct research under the NIH Visiting Program. In FY 98, 72 Visiting Associates, 87 Visiting Fellows, 42 Special Volunteers, and 17 Visiting Scientists participated in joint research in the Division of Intramural Research, NHLBI. Countries and areas represented included Argentina, Australia, Austria, Canada, Chile, China, Denmark, Finland, France, Germany, Greece, Hungary, India, Iran, Israel, Italy, Japan, Korea, Morocco, the Netherlands, Nigeria, the Philippines, Poland, Russia, Slovenia, South Africa, Spain, Sweden, Thailand, Turkey, Ukraine, the United Kingdom, and Taiwan.

XVIII.

National Human Genome Research Institute

INTRODUCTION

The National Human Genome Research Institute (NHGRI) was established in 1989 to lead the effort of the National Institutes of Health (NIH) in the Human Genome Project. NHGRI's Division of Extramural Research funds Human Genome Project research in laboratories throughout the country. Research on genetic and physical mapping, DNA sequencing, database development, and technology development for genome research, as well as studies of the ethical, legal, and social implications of genetics research, are supported by the extramural arm of NHGRI. In February 1993, the Institute expanded its role at the NIH by establishing the Division of Intramural Research, a cutting-edge program that (a) translates the tools of the Human Genome Project into knowledge about human genetic disease and its diagnosis and treatment and (b) serves as the hub for human genetics research at the NIH.

NHGRI, through its extramural and intramural research programs, contributes to identification of genes involved in human disease and study of the function of these genes and their products. The Human Genome Project provides data, material resources, and technology that will improve the ability of scientists to conduct biological research rapidly, efficiently, and cost-effectively. This infrastructure has already dramatically accelerated the study of human inherited disease. In the laboratories of the Division of Intramural Research, with the tools produced by the Human Genome Project, scientists are developing and using the most advanced techniques to study the fundamental mechanisms of inherited and acquired genetic disorders.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Progress on Human Genome

An international collaborative effort is scheduled to produce the first complete, highly accurate sequence of the human genome by the end of 2003. In the United States, scientists at several sequencing centers around the country who are supported by NHGRI, together with scientists supported by the U.S. Department of Energy, will sequence 60%–70% of the 3 billion base pairs in the human genome. The rest of the human genome will be sequenced at the Sanger Centre, Cambridge, England, which is funded by the Wellcome Trust, and at other sequencing centers around the world.

Gene Map of Human Genome

More than 100 scientists from government, universities, and commercial laboratories around the world have compiled a gene map, which represents the Human Genome Project's most extensive effort so far to locate and identify the approximately 80,000 genes in the human genome. The map includes more than 30,000 gene tags. It now gives hunters of disease genes who have narrowed their search to a specific region on a chromosome about a 40% chance that the gene they are looking for already has been characterized by this effort. An electronic version of the gene map organizes the details into a readily accessible Internet site (www.ncbi.nlm.nih.gov/genemap) with extensive links to supporting data about the DNA structure of the genes and the proteins they encode.

Completion of *Caenorhabditis elegans* Genome

The complete sequence of the 100 million base pairs in the genome of the roundworm *Caenorhabditis elegans* was published in December 1998. The sequencing was carried out as a collaborative effort between Washington University, St. Louis, Missouri (supported by NHGRI), and the Sanger Centre, Cambridge, England. *C. elegans* is an important model organism for studying development and is the first multicell animal with a genome that has been sequenced. Data on the project are available on the Internet at http://genome.wustl.edu/gsc/.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Extramural Programs

In addition to support for the sequencing of the U.S. portion of the human genome, NHGRI continues to fund a portion of an international consortium involved in the *Saccharomyces* Genome Deletion Project. This project aims (1) to generate a complete set of yeast mutants resulting from deletion of genes and (2) to assign functions to the genes by studying the mutants.

International Databases

The NIH provided the sole support for the following international databases: Mouse Genome Database; SacchDB (yeast, *Saccharomyces cerevisiae*); OMIM (Online Mendelian Inheritance in Man); and GenLink (Human Genetic Linkage Database). The Flybase (*Drosophila melanogaster*) is supported by the NIH and the British Medical Research Council.

The Mouse Genome Database and Flybase are maintained locally by institutions in Australia, France, Japan, and the United Kingdom. A Flybase site is maintained locally in Israel.

International Meetings

NHGRI provided support for the following international meetings in fiscal year 1998 (FY 98):

- International Strategy Meeting on Human DNA Sequencing, in Bermuda, in February 1998;
- Zebra Fish Development and Genetics Conference, in Cold Spring Harbor, New

York, in May 1998;

- Genome Mapping and Sequencing Conference, in Cold Spring Harbor, in May 1998;
- International Conference on Intelligent Systems for Molecular Biology, in Montreal, Quebec, in June 1998;
- Conference on Chromatin Structure and Function, in Tilton, New Hampshire, in July 1998;
- 6th Small Genomes Conference, in Arrowhead, California, in September 1998;
- Conference on Mouse Molecular Genetics, in Cold Spring Harbor, in September 1998; and
- Conference on Mouse Functional Genomics, in Miami, Florida, in October 1998.

In FY 98, NHGRI supported the following courses available to international investigators:

- Advanced Genome Sequence Analysis Course, in Cold Spring Harbor, in March 1998;
- Genetic Analysis Methods for Medical Researchers, in Durham, North Carolina, in April 1998;
- Training in Sequence Analysis Using Supercomputers, in Pittsburgh, Pennsylvania, in July 1998; and
- Advanced Linkage Analysis Courses, in New York, New York, in September 1998.

NHGRI staff also participated in the following international meetings:

- Workshop on Global Assessment of R&D (research and development) Status and Trends in Nanoparticles, Nanostructured Materials, and Nanodevices, in Arlington, Virginia, in February 1998;
- 10th International Genome Sequencing and Analysis Conference, in Miami Beach, Florida, in September 1998;
- 5th International Conference on Automation in Mapping and DNA Sequencing, in St. Louis, Missouri, in October 1998; and
- Medical Research Council Workshop on Sequencing the Mouse Genome, in London, England, in October 1998.

During FY 98, NHGRI staff met with representatives of government, industry, and academic institutions from various countries, including Brazil, China, Finland, Japan, and the United Kingdom.

Intramural Programs and Activities

West African Origins of Type 2 Diabetes Mellitus in African Americans

Through the support of the NIH Office of Research on Minority Health, NHGRI and Howard University, Washington, D.C., started the pilot phase of the African-American Diabetes Mellitus Study in January 1997. This pilot study of genetic susceptibility to non–insulin-dependent diabetes (type 2 diabetes) in people of African descent is completed, and expansion to a full-scale study is under way. Through collaboration with Howard University and five recruitment centers in West Africa, the scientists obtained urine, blood for DNA extraction, and clinical data from 75 sibling pairs with type 2 diabetes, in an effort to identify genes leading to susceptibility to this disease. In the full-scale study, which began in 1998, the scientists will analyze 240,000 genotypes from 400 sibling pairs with type 2 diabetes.

Hereditary Prostate Cancer

NHGRI has initiated a collaborative effort with scientists in Tampere, Finland, to explore the genetics of hereditary prostate cancer (HPC). To facilitate the identification of a gene or genes involved in HPC, investigators are identifying Finnish families with multiple cases of prostate cancer. Because of the unique population history of Finland, Finnish patients are likely to share a common ancestral mutation predisposing them to HPC. A shared ancestral mutation would in turn make it possible to use studies of inheritance to pinpoint the location of this gene in the human genome. A gene predisposing to HPC in U.S. families (HPC1) was recently identified on chromosome 1. The Finnish study facilitated identification of a second locus on chromosome X. This HPC-X locus may cause up to 40% of HPCs in the Finnish population.

Hereditary Breast Cancer

NHGRI has initiated a collaborative effort with scientists in Tampere and Helsinki, Finland, and in Lund, Sweden, to explore the genetics of hereditary breast cancer. Genetic epidemiologic evidence indicates that the two known genes that predispose a person to developing breast cancer (BRCA1 and BRCA2) have a role in only about 15%–30% of families with hereditary breast cancer in these populations. This finding suggests that a third, unknown, susceptibility gene (BRCA3) is often involved. To facilitate the identification of a new gene or genes involved in hereditary breast cancer, the investigators have obtained data on and obtained DNA samples from many families in Finland and Sweden who do not have the BRCA1 or BRCA2 gene. High-throughput fluorescent genotyping is performed at NHGRI to search for new loci involved in genetic predisposition to breast cancer.

Finnish-U.S. Investigation of Type 2 Diabetes Mellitus

The Finland-U.S. Investigation of Non–Insulin-Dependent Diabetes Mellitus is a genetic study to find genes that predispose persons to develop type 2 diabetes and related phenotypes, in a Finnish population. A genome scan has now been completed on DNA from 2,401 persons. More than 1.3 million genotypes have been generated, and the average error rate is 0.12%. This research has shown evidence for linkage to type 2 diabetes on both arms of chromosome 20, and some evidence for linkage on the long arm of chromosome 11 also exists. In the second phase of this study, the scientists have obtained an additional 2,916 DNA samples from other affected persons and members of the extended family. They will undertake further analyses of linkage and of linkage disequilibrium on all the DNA samples, to narrow down intervals for eventual positional cloning of diabetes genes.

Tissue Microarray Technology

NHGRI has initiated a collaborative effort with scientists at the University of Switzerland, Basel, to develop technology for high-throughput molecular profiling of very large numbers of cancer specimens. The Pathology Institute, Basel, has more than 150,000 archival samples of tumor tissue and approximately 4,000 freshly frozen samples. Up to 3,000 specimens will be selected for analysis. The tumor tissue microarray technology, developed at NHGRI, enables a high-throughput analysis of molecular alterations in cancer cells at the DNA, RNA, or protein level. Up to 1,000 tumor specimens can be evaluated in a single experiment.

Oral Clefts

NHGRI collaborates on a study of the genetics of oral clefts (cleft lip, cleft palate, or both) with investigators in Syria. Researchers collect family history, clinical data, and blood samples from persons whose families have several members affected with oral clefts, without the presence of a well-known genetic syndrome. DNA from the blood samples will be genotyped, and NHGRI scientists will perform statistical analyses by using these data, together with family history and clinical information, to determine whether there is evidence of genetic susceptibility to oral clefts. For any genetic areas tentatively identified, there will be additional investigation with the use of a dense map of genetic markers and further statistical analyses. The chromosomal regions most likely to contain an area that increases risk for oral clefts will be investigated with molecular genetic techniques designed to clone and sequence the gene in question. To date, several hundred persons have been studied in Syria, and genotyping of the first set of families is scheduled to begin in the near future.

Parkinson's Disease

NHGRI researchers collaborate with neurologists at the University of Patras, Greece, in a study of familial Parkinson's disease. Early-onset Parkinson's disease rarely occurs repeatedly in families. It usually occurs as an isolated case in families in which the hereditary contributions to susceptibility are numerous and complex and their effects are obscured by environmental factors. Scientists study the rare families with the strongly inherited early-onset form of disease, in an effort to identify additional genes that, when altered, can cause Parkinson's disease. They are also examining isolated populations in Greece that include multiple patients with Parkinson's disease. Isolated populations are likely to carry only a subset of the genes that predispose to the common forms of Parkinson's disease, making these factors easier to study and identify.

XIX.
National Institute of Mental Health

INTRODUCTION

The National Institute of Mental Health (NIMH) creates a firm scientific foundation for the clinical care of mental disorders by supporting research on the understanding, diagnosis, prevention, and treatment of mental illnesses and by exchanging information nationally and internationally with all relevant individuals and organizations to improve the state of mental health knowledge and its application. The Institute supports research through its extramural and intramural programs. Extramural scientists, working in research facilities around the country and internationally, are awarded grants to conduct research. General research areas include molecular and behavioral neuroscience; psychopharmacology; drug development; cognitive processes; personality, emotion, and psychosocial processes; factors influencing behavioral development and modification; biological, psychological, and psychosocial aspects of stress and other psychological states; behavioral medicine; psychoimmunology; and research in acquired immunodeficiency syndrome (AIDS). The study of distinct mental disorders is supported by research and research training in epidemiology, etiology, and disease prevention, diagnosis, and treatment.

In the developing world, where four-fifths of the global population live, the prevalence of noncommunicable diseases is increasing rapidly. Psychiatric disorders constitute a highly significant aspect of global disease burden when both disability and death are taken into account. According to *The Global Burden of Disease*, by 2020, unipolar major depression is expected to be the second leading cause of this burden, as measured by disability-adjusted life years. (Disability-adjusted life years are the years of healthy life lost because of the combined effect of disability and mortality from disease, injury, and risk factors.) Psychiatric and neurological conditions could increase from 10.5% of the total global disease burden in 1990 to 15% in 2020—a larger increase than for cardiovascular disease. Other causes of illness that have a behavioral and mental health component are transmission of human immunodeficiency virus (HIV) and other sexually transmitted diseases (STDs), tobacco use, intentional injuries, lifestyles contributing to chronic illnesses, and perinatal problems.

NIMH supports research and research training in delivery of services within the mental health system; provision of mental health services in other types of health care settings; economic factors influencing supply, demand, and costs of mental health services; mental health issues related to antisocial and violent behaviors; and legislation on disabilities related to mental disorders.

The NIMH research support programs are organized under one intramural and three extramural research divisions: the Division of Intramural Research Programs; the Division of Basic and Clinical Neuroscience Research; the Division of Services and Intervention Research; and the Division of Mental Disorders, Behavioral Research, and AIDS. Scientists from other countries collaborate in research activities and share information with these divisions.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Russia

In September 1997, the Health Committee of the U.S.-Russia Joint Commission on Economic and Technological Cooperation endorsed its joint mental health work group's recommendations for developing two program areas. These two areas include the reduction of disability associated with major depressive illness in primary care settings and focusing greater attention on the mental health consequences of disasters due to either natural or human causes. The continuing U.S.-Russia Joint Commission on Economic and Technologic Cooperation is now known as the Gore-Primakov Commission, formerly the Gore-Chernomyrdin Commission. The Health Committee is cochaired by the Secretary of the U.S. Department of Health and Human Services (DHHS) and the Russian Minister of Health.

Collaboration between primary health care providers and mental health specialists, to reduce disability associated with depression, was inspired by the publication of *The Global Burden of Disease* by the World Bank and the World Health Organization (WHO). In an independent assessment of the human and economic costs of disease, this groundbreaking study has helped health care professionals to refocus efforts on the consequences of disability from chronic diseases and on premature mortality. The Director of the National Institutes of Health (NIH), the Director of NIMH, and the entire NIH community have taken this approach very seriously as an important dimension for planning the use of health care resources, both services and research.

With the finding that mental disorders in general and major depression in particular are leading causes of disability worldwide, the joint mental health group concluded that this public health burden could best be reduced by joint efforts among primary care and mental health specialists, particularly medical psychiatrists, but also psychologists, nurses, and social workers. Making the cooperation of primary care providers and mental health specialists work more effectively for the management of chronic diseases is a relatively new area of emphasis for both Russia and the United States. Such efforts need not be limited to mental health conditions.

When the U.S. members of the joint mental health work group visited Moscow in September 1997, they observed the interaction of primary care and mental health specialists in two polyclinics. Since then, Russian scientists have enlisted the support of additional polyclinics in Moscow and in Dubna, Tomsk, and Yaroslavl. Representatives from these polyclinics completed a 1-week visit to the University of Washington, Seattle, where they could observe and evaluate several model programs for initiating screening and for diagnosis and treatment of depression in primary care settings with various types of collaboration involving psychiatrists. A researcher in the university's Department of Psychiatry coordinated a discussion with colleagues from Kaiser Group Health, Puget Sound, Washington, and the Dean Clinic, Madison, Wisconsin.

After 3 days of discussions in Seattle, the Russian group developed detailed protocols for screening and confirming diagnoses, as well as two treatment models with clear criteria for monitoring symptoms, level of disability, and treatment outcome. In addition to the important funding from the U.S. Agency for International Development (USAID) to launch this project, the effort is now also supported by the NIH Fogarty International Center (FIC); WHO; the World Psychiatric Association; NIMH research grantees; Eli Lilly; and Pfizer. Such diversified support is a major strength of the program as it moves into a pilot demonstration of services in fiscal year 1999 (FY 99).

Recent intensive evaluations of joint treatment programs compared with usual care have yielded convincing evidence that both symptoms and the number of days lost from work because of disability can be substantially reduced in the collaborative care model, by using treatment guidelines for both primary care physicians and psychiatrists. The Agency for Health Care and Policy Research and the American Psychiatric Association provide guidelines for primary care professionals and psychiatrists, respectively, for handling the more complex cases of depression. In the model, patient care is monitored by coordinators who assess the quality of care and patient outcome. This model has been used at the University of Washington for management of other chronic diseases such as diabetes, in Seattle.

During FY 98, NIMH-funded researchers in Moscow developed educational programs in Moscow, Dubna, Tomsk, and Yaroslavl, to help primary care providers to recognize depression. They worked with WHO to develop a major public education program on depression and other mental disorders in Russia. The program, entitled Nations for Mental Health, is scheduled to start in June 1999. To assist in international communication, the researchers have translated English-language textbooks on mental health into Russian. These books include the well-known Kaplan and Sadock *Manual in Clinical Psychiatry*—a project the previous Russian Minister of Health considered sufficiently important to edit herself.

After the February 1998 visit of 10 Russian psychiatrists and primary care physicians for an intensive training program at the University of Washington, Seattle, the head of the Russian delegation returned to Moscow to assemble a final protocol and initiate a pilot demonstration program on the treatment of depression at primary care sites. During a visit to Russia in the fall of 1998, two NIMH investigators and a WHO staff member evaluated the progress of the research teams in implementing the protocol. In view of the economic circumstances in Russia, the progress has been impressive. Teams have been established at five polyclinics in Moscow, two outpatient programs in Dubna, and two outpatient polyclinics in Yaroslavl. There has also been a request from a former Minister of Health to expand the program to include the city of Tomsk, and a physician from Siberia has asked to participate.

Because of the rapid development of the teams of psychiatrists, primary care physicians, and nurse coordinators, it is possible to begin the next phase of this demonstration project. The model includes the following components:

- screening for specific acute or chronic disorders;
- administration of initial therapy according to a treatment protocol, by a specialist (e.g., a psychiatrist) working closely with the primary care clinician, with long-term management by the primary care physician;
- reliance on a nurse–patient coordinator to ensure adherence to the "evidence-based" protocol; and
- measurement of change in symptoms and level of ability to function.

This model is appropriate for any chronic disease, such as hypertension, diabetes, chronic obstructive pulmonary disease, or ischemic heart disease. Implementation of the model requires programs to provide relevant education to primary care physicians and mental health specialists and joint efforts to form consensus on the treatment protocols; education of patients to encourage acceptance of treatment; and public education to change the general understanding of stigmatized disorders in particular.

Funding for some aspects of this project was provided by USAID through the DHHS Office of International and Refugee Health. WHO is also considering a related cabinet-level project on mood disorders that would use the Russian experience as a model for actually reducing disability-adjusted life years associated with one of the major disorders presented in *The Global Burden of Disease.* In addition, to help support the coordination of research for this project in Moscow, NIMH will encourage grantees to apply through FIC for funding to extend U.S. primary care research studies on mental health that include Russian investigators.

Revision of *International Classification of Impairments, Disabilities, and Handicaps*

Throughout FY 98, the International Task Force on Mental Health and Addictive, Behavioral, Cognitive, and Developmental Aspects of the *International Classification of Impairments, Disabilities, and Handicaps* (ICIDH) continued its active participation under the chair, the Assistant Director of Disability Research, Division of Services and Intervention Research, NIMH. This international task force is charged with the mental health aspects of the revision of the WHO ICIDH, which classifies the effects of disorders, traumas, and congenital anomalies in three areas:

1. the structure and function of the human body and bodily systems;
2. the purposeful activities in which people engage; and
3. the involvement of people in life situations.

The international task force members essentially completed field trials of the beta-1 version of ICIDH-2. Included in the five mandatory field trials was the translation and linguistic analysis of beta-1 ICIDH-2. The task force is responsible for translation into Russian, Tamil (Indian language), Turkish, and Yoruba (Nigerian language).

In addition to the five mandatory field trials, the task force first conducted a study to examine the cultural similarities and differences between opinions of mental health experts in Japan and the United States on ICIDH-2 items and their definitions. This study was supported by a short-term fellowship from the Japan Society for the Promotion of Science. Second, the task force performed a child's version of one of the field trials, obtaining conceptual feedback on disabilities from school-age children. Third, the task force conducted a survey of Olympic parathletes on their response to disablements as defined in ICIDH-2. Finally, the task force convened experts on the Spanish language and culture to translate ICIDH-2 into Spanish and formed a Spanish network for future participation in activities related to ICIDH-2.

Office of AIDS Research: Prevention Program

Research grants with a foreign component supported by the NIMH Office of AIDS Research have bidirectional goals: to corroborate work conducted in the United States; to extend the generalizability of research findings to other multicultural settings; and to develop new understandings of the dynamics of AIDS prevention.

NIMH supports three AIDS Research Centers that actively promote international research. For 10 years, the Center for AIDS Prevention Studies (CAPS) at the University of California, San Francisco, has supported an international program in Africa, Asia, Eastern Europe, and Latin America. Studies include the following:

- a randomized control intervention trial of an AIDS prevention program with adult night-school students in São Paulo, Brazil, resulting in a significant increase in condom use with the secondary sexual partners of young women but no increase in condom use with the primary partners;
- a feasibility study of using traditional youth organizations as a venue for AIDS prevention programs that target young persons who are in or out of school, in Bali, Indonesia; and
- a descriptive study of male adolescents living in rural areas along the Trans-African highway in Kenya who have sexual relations with resident sex workers and of female adolescents who have sexual relations with truck drivers.

CAPS is proposing 50 joint AIDS projects in which a CAPS expert in AIDS prevention would partner with an investigator in a foreign country to conduct a culturally appropriate study.

The NIMH-supported HIV Center for Clinical and Behavioral Studies at Columbia University, New York City, New York, has a history of joint research in Brazil, Puerto Rico, and South Africa. Both NIMH and FIC are contributing to efforts to build research capacity in South Africa. These efforts, which had focused on HIV and AIDS epidemiology in South Africa, have expanded to include social and behavioral science and studies in Botswana and Namibia. Joint activities include the following research:

- a study of young persons in boarding schools in Namibia, which is evaluating the effects of a manualized intervention to reduce HIV-related risk behaviors;
- a behavioral intervention study of men and women seeking care in STD clinics in Durban, Kwazulu, Natal, South Africa; and
- testing of a program for culturally oriented prevention of STD in migrant laborers in Kwazulu, to determine the effects on HIV and STD incidence.

The Center for AIDS Intervention Research, Milwaukee, Wisconsin, has recently begun collaborative studies in St. Petersburg, Russia. The research team has identified an alarming prevalence of STDs and HIV among young persons, and prevention programs are being planned.

Research Grants

An NIMH study of 600 female sex workers, 500 clients, and 150 pimps in Bali, Indonesia, is evaluating the effectiveness of two long-term programs to maintain safer HIV- and STD-related behaviors. The results will be assessed at 6-, 12-, and 18-month intervals. The presence of sexually transmitted infections will be evaluated at baseline and at the three follow-up visits. Personal interviews will also be used to obtain qualitative and quantitative data, in efforts to understand the dynamics of disease transmission in this high-risk group. The findings from this project can be used to develop long-term intervention programs for the sex workers, clients, and pimps. This group represents a major route of STD transmission in some developing countries.

The NIMH HIV/STD prevention program supports a study in Uganda that is collecting ethnographic, survey, and epidemiologic data, to identify the socioeconomic determinants of HIV in adolescents in Uganda. The investigator is examining the dynamics of transmission that explain the dramatic difference in HIV rates for females aged 14–18 years, who are six times more likely to be HIV positive than are males in this age group. Gender-related factors (e.g., physiological and biological differences) and cofactor variables (e.g., ulcerative genital tract disease) may increase the risk of HIV for females compared with that for males, but they do not fully explain the higher rates for females. The variables affecting gender-specific risk need to be elucidated before effective prevention programs can be tailored to the needs of girls and women.

International Meetings

The Office of AIDS Research convened a group with expertise in international research to prepare a consensus statement on the role of NIMH support of international studies. This group determined that the United States has a vital and direct global interest in health, which derives from a long and enduring tradition of humanitarian concern and enlightened self-interest. Because of international mobility, disease and illness respect no political borders. Furthermore, the health and welfare in one country can lead to internal economic and political instability and global conflict that has a cascading effect on international security. U.S. expertise in science and technology can continue to benefit global health, and international collaboration can lead to scientific advances in biomedical and behavioral research. The group of experts recommended areas in which behavioral prevention research on HIV and STD might have mutual benefits to the United States and host countries. These recommendations were presented to the Director, Office of AIDS Research, and the Director, NIMH, and became part of the report to the NIMH National Advisory Mental Health Council.

The 6th NIMH Conference on the Role of Families in Preventing and Adapting to HIV/AIDS was held in Washington, D.C., on July 29–31, 1998. To encourage international participation, an investigator from City University, London, England, served as a member of the planning group for this conference, which has always had an international component. An investigator from Calcutta, India, reported success in motivating commercial sex workers to seek other work, by influencing their families to encourage them to do so. A pediatrician at Natal University, Durban, South Africa, addressed the conference on the importance of families in prevention and treatment of HIV disease. (This investigator is the chair of the XIIIth International AIDS Conference, to be held in Durban, South Africa, in the summer of 2000. NIMH grantees performing research on the role of families in prevention of HIV disease are planning to submit several symposia to this conference.) A researcher from Institut Universitaire de Médecine Sociale et Préventive, Geneva, Switzerland, lectured on the effect of migration on HIV transmission. Another researcher, from the AIDS Family Caring Trust, Mutare, Zimbabwe, presented a model for care of orphans of parents who have died of AIDS. These orphans are an increasing critical problem in countries with a mature AIDS epidemic. These presentations greatly enhanced the quality of the conference and developed networks that can lead to other joint efforts in the future.

Future International Research

NIMH was the lead Institute in development of a Joint Statement on Indo-U.S. Collaboration on Prevention of Sexually Transmitted Diseases and HIV/AIDS. The current plan is to have the statement signed by the Secretary of DHHS and the Director General of the Indian Council on Medical Research, at the meeting of the World Health Assembly, in Geneva, Switzerland, in May 1999. NIMH will send a delegation of 13 U.S. scientists to New Delhi, India, in January 1999, to finalize plans for joint research projects.

In addition, the NIMH Collaborative HIV/STD Trial is being planned. It is anticipated that four grants will fund research teams at four sites in Africa, Asia, Eastern Europe, and South America and that one grant will support a Data Coordinating Center. A protocol based on the public opinion leader model, a highly successful preventive intervention program, will be jointly developed to prevent the further spread of HIV among high-risk populations in various cultural settings.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

South Africa

In February 1998, at the request of the Director of Mental Health and Substance Abuse in South Africa, researchers from Duke University, Durham, North Carolina, Drew University Medical School, Los Angeles, California, and NIMH participated in a 2-week consultation in South Africa. This meeting was also held in response to an earlier request from the Minister of Health for consultation on the development of effective community care for patients who have been provided largely custodial care in hospitals. In keeping with the plan to improve health care to ensure basic human rights to all persons, South Africa is engaged in grassroots democratic efforts to help communities to develop effective community care for persons with severe mental illnesses. Consultation on community care was provided at Tower Hospital, Fort Beaufort, Eastern Cape Province, and at Madedeni Hospital, Newcastle, Kwazulu, Natal.

At the request of staff from the Medical University of South Africa, Pretoria, Gauteng Province, the researchers also presented a seminar and consulted with faculty, psychiatric residents, and medical students at the medical university about research on mental health, health care services, and HIV/AIDS and about potential areas for joint research on mental health. Earlier in February, a group from the Medical Research Council, the medical university, and other universities came to NIMH to consult with Institute staff on mental health research and research development. The group had been participating in a meeting on Substance Abuse Prevention and Treatment, at Howard University, Washington, D.C., in February.

The Minister of Health, Eastern Cape Province, participated in the 12th International Conference on Mental Health Problems in the General Health Care Sector, entitled Effectiveness of Interventions in Primary Care, in Baltimore, Maryland, on July 13–14, 1998. She also consulted with the U.S. Surgeon General and with staff from the DHHS Office of International and Refugee Health, the NIH, and NIMH.

NIMH Working Group on the Mental Health Consequences of Torture and Related Violence and Trauma

In the summer of 1997, NIMH assembled a panel of international experts (a) to produce a report on the status of scientific knowledge on the mental health consequences of torture and related trauma and violence and (b) to make research recommendations based on this knowledge, which would have implications for treatment, services, and policy development for survivors of torture. The report was stimulated by representatives of South Africa who attended a multidisciplinary multiagency research conference on Survivors of Torture, in Washington, D.C., in April 1997. The meeting was cosponsored by NIMH, the DHHS Office of Refugee Resettlement, the Center for Mental Health Services (U.S. Substance Abuse and Mental Health Services Administration), and a U.S. senator. The South African delegates asked the Director, NIMH, for assistance in obtaining scientific information on the mental health consequences of torture. They thought such information would be a major contribution to the field in general and to South Africa in particular, as it began its healing process after the end of apartheid. In response to this request, the NIMH Working Group on the Mental Health Consequences of Torture and Related Violence and Trauma was established.

In March 1998, NIMH transmitted a preliminary Report on the Mental Health Consequences of Torture and Related Violence and Trauma to members of the South African Truth and Reconciliation Commission and Archbishop Desmond Tutu. The report will be available to a wide range of individuals and countries who struggle with the consequences of torture, violence, and related trauma.

South African Medical Research Council and Truth and Reconciliation Commission

In October 1998, the Chief of Psychology Services, Boston University School of Medicine, Massachusetts, was contracted by NIMH to travel to South Africa (a) to present a series of talks on the content of the NIMH Report on the Mental Health Consequences of Torture and Related Violence and Trauma; (b) to attend and make a presentation at a scientific conference on Mental Health in

South Africa After the Truth and Reconciliation Commission, sponsored by the Medical Research Council of South Africa; and (c) to participate in a series of meetings with academic departments of psychiatry, psychology, sociology, and social work; state and private mental health practitioners; and members of the Medical Research Council and the Truth and Reconciliation Commission of South Africa. These presentations and discussions focused on reviewing and highlighting findings of the NIMH scientific report and on the expertise of the Chief of Psychology Services with clinical research on patients exposed to trauma.

Mental Health Consequences of Apartheid and Torture

A Request for Proposals for Research on the Mental Health Consequences of Torture: Its Treatment and Rehabilitation was issued by NIMH in February 1998. Several persons from South Africa, in cooperation with researchers from the University of Michigan, Ann Arbor, and Harvard University, Boston, Massachusetts, submitted a research application entitled Torture and Mental Health in South Africa. The 5-year research grant was awarded to the University of Michigan. The direct cost in the 1st year is $300,064, and the estimated total cost for the 5-year study is $2,433,006.

This grant will support an epidemiologic survey of the prevalence and mental health consequences of torture in South Africa. The investigators will consider the psychological sequelae of violent acts for both perpetrators and survivors. The survey will be carried out in close collaboration with senior investigators that include the Dean of South Africa's School of Public Health; the director of the first national survey of psychiatric disorders in the United States; commissioners of the Truth and Reconciliation Commission in South Africa; and experts on survey research from the University of Michigan.

Activities With International and Multinational Organizations

International Cooperative Biodiversity Group Program

For the past 4 years, NIMH has contributed funds to support the international research on biodiversity and drug discovery of the International Cooperative Biodiversity Group (ICBG) Program. The ICBG Program is an innovative, interagency conservation and development program administered by FIC. The goal of the Program is to promote biodiversity conservation and sustained economic activity through the discovery and development of therapeutic agents derived from natural products (plants, animals, and microbes). The ICBGs consist of partnerships among public institutions, pharmaceutical companies, and environmental organizations. This unique 5-year program is jointly funded by USAID, the National Science Foundation, and Institutes of the NIH: FIC; the National Cancer Institute; the National Heart, Lung, and Blood Institute; the National Institute of Allergy and Infectious Diseases; and NIMH.

Megascience Forum

NIMH staff, together with staff of other Federal agencies, have participated in the Megascience Forum through a Working Group on Biological Informatics. The Megascience Forum was established by the Organization for Economic Cooperation and Development, based in Paris, France. This working group is led by the United States and is chaired by staff from the National Science Foundation. The two subgroups are Biodiversity Informatics, which is chaired by the Smithsonian Institution, Washington, D.C., and Neuroinformatics, which is chaired by NIMH.

U.S.-European Commission

An NIMH neuroscience staff member serves as the representative of the NIH to the U.S.-European Commission (U.S.-EC) Task Force on Biotechnology Research. Under the auspices of the task force, a Neuroinformatics Steering Group was established to implement recommendations that were formulated at an international workshop in September 1995. The intent of these recommendations is to promote research interaction and collaboration across neuroscience and informatics disciplines and between the United States and the European Union. Some of the short- and intermediate-term goals have been accomplished.

At the 8th Meeting of the U.S.-EC Task Force on Biotechnology Research, in Brussels, Belgium, in September 1998, it was agreed that the members of the Neuroinformatics Steering group would be increased to five or six from Europe and an equal number from the United States, thus allowing greater representation from the diverse fields involved in this area of research. In addition, the first meeting of this new group would concentrate on initiating training efforts with special attention to new researchers. Other issues to be discussed would include the value of starting joint international neuroinformatics demonstration projects and the need for neuroinformatics workshops.

WHO-NIH Joint Research Project

In collaboration with NIAAA and NIDA, NIMH continued during FY 98 to build on the strategies for development of research methods and on the research support network created with WHO, to produce two instruments for the assessment of disablement, for use in clinical and epidemiologic research. This project is nearly halfway through its 5-year time line. In 18 centers in 15 countries, formative testing is being performed to validate the psychometric properties of the instruments. During FY 98, NIAAA, NIDA, and NIMH awarded a supplement for development of a measure of disability that is based on empirical assessment and that can be used to estimate global burden in terms of disability-adjusted life years.

An NIMH researcher has accepted an invitation to chair the new Mental Health Economics Section of the World Psychiatric Association. In this capacity, she is responsible for organizing regional and world meetings on research and policy on mental health economics and for providing members of the World Psychiatric Association with educational materials on related issues.

During FY 98, this researcher continued her work as editor-in-chief of the international interdisciplinary *Journal of Mental Health Policy and Economics*. The first three issues of the journal have been well received by the research community.

Extramural Programs

Fellowships

Two predoctoral students and one postdoctoral fellow funded by NIMH have chosen to work in laboratories in Canada and the United Kingdom to pursue subspecialties in neuroscience with mentors and technologies unique to these international research sites.

Two of the investigators are pursuing

clinical neuroscience specialties. One investigator, at the University of Alberta, Edmonton, is studying the cellular basis of eating behavior, by investigating the interaction in the lateral hypothalamus of an anorectic peptide (melanin-concentrating hormone) with a hormone that stimulates eating (neuropeptide Y). Another researcher, at the University of Ottawa, Ontario, is focusing on the psychophysiology of cognition during sleep in populations disabled by head injury, chronic pain, aging, or sleep deprivation.

Another researcher in basic neuroscience at the University of London, England, is learning to use nuclear magnetic resonance to image the differences in calcium metabolism that distinguish normal brain cells from cells in malignant brain tumors.

The Assistant Director for Disability Research, Division of Services and Intervention Research, NIMH, completed a short-term fellowship from the Japan Society for the Promotion of Science. The purpose of the fellowship was to refine analyses of cross-cultural data on disablements due to mental health conditions. A focus group of Japanese mental health experts was convened in Tokyo to examine quantitative data collected in conjunction with the revision of WHO's ICIDH from an explicit cultural perspective and to interpret the data. The draft ICIDH-2 underwent international field trials to ensure sensitivity, relevance, and usefulness (a) to policy makers; (b) to providers of health care and care of persons with disabilities; (c) to persons with disabilities and their families; and (d) to advocates for persons with disabilities worldwide. The outcome supported the usefulness of cultural interpretation of international data sets in general and the revision of ICIDH in particular.

Research Grants

Research on the Psychosocial Impact of Trauma on Bosnian Refugees entails a large-scale, population-based study. Investigators are examining the effects of personal, environmental, and other risk factors on the relationships among trauma, psychiatric symptoms, and functional status. The study will produce data on psychiatric follow-up in a refugee population, allowing examination of dose–effect relationships among trauma, psychiatric symptoms, and functional status and evaluation of the ability to earn a living before and after repatriation. By analysis of data on the duration and character of the dose–effect relationships, the proposed research fills a major gap in efforts to understand the effect of trauma on the ability to function and to participate in economic activity.

The Neuroinformatics Office, NIMH, funds a grant to an international consortium of investigators conducting neuroinformatics research on probabilistic approaches for visualizing and analyzing three-dimensional data sets, such as those obtained from use of various neuroimaging modalities. The study is entitled Probabilistic Reference System for the Human Brain. The consortium includes investigators at the Montreal Neurological Institute, McGill University, Quebec. In FY 98, for the first time, automated probabilistic tools were used at McGill University to analyze data from a phase III clinical trial of a new therapy for multiple sclerosis. This new capability will allow powerful statistical tools to be brought to bear on important clinical issues.

A Request for Application was issued to solicit large-scale, collaborative, multidisciplinary research projects to identify genes involved in schizophrenia and mood disorders. Two of the funded applications have major international components. A scientist at Harvard Medical School, Boston, Massachusetts, is collaborating with scientists at Sun Yat-Sen University of Medical Sciences, Guangzhou, China, and National Taiwan University Hospital, Taipei, where large numbers of pedigrees containing multiple individuals affected with schizophrenia will be obtained. An investigator at Columbia College of Physicians and Surgeons, New York City, New York, is collaborating with scientists at Hadassah-Hebrew University Medical Center, Jerusalem, Israel, where a large number of pedigrees containing multiple individuals affected with bipolar disorder will be obtained. The large numbers of cohesive extended families in China, Israel, and Taiwan will result in pedigrees that have increased power for genetic analyses. These projects are expected to greatly complement ongoing human genetics projects on schizophrenia and bipolar disorder that analyze pedigrees obtained in the United States.

In collaboration with the National Public Health Institute, Helsinki, an investigator at the University of Pennsylvania, Philadelphia, is studying brain function and structure in twins with schizophrenia in Finland. Schizophrenia is known to be heritable, and there is much evidence to suggest that the condition involves developmental abnormalities of the brain. A unique and powerful way to investigate the interaction of these two factors is to study monozygotic twins who are discordant for the illness. Finland offers unique research opportunities for such studies because the government maintains detailed registries of twins and of patients with schizophrenia.

In a project entitled The Hippocampal Interneuronal Network, a researcher at the Center for Molecular and Behavioral Neuroscience, Rutgers State University of New Jersey, New Brunswick, is examining the anatomy and physiology of inhibitory interneurons in the hippocampus. The scientist brings specific and unique expertise to the project through collaboration with researchers at Institut Pasteur, Paris, France, and the Institute for Experimental Medicine, Budapest, Hungary. To reveal the connectivity patterns of hippocampal inhibitory interneurons, the study combines dual intracellular recording from functionally connected neurons in the hippocampus with intracellular staining and sophisticated immunocytochemical double-labeling techniques. The French researcher provides expertise in the technique of dual intracellular recording in the hippocampus, and the Hungarian researcher is world renowned in use of immunocytochemical techniques.

A researcher at the National Institute of Mental Health and Neurosciences, Bangalore, India, received an NIMH grant for study of Psychoactive Drug Metabolism by Brain Cytochromes P-450. The aims of the research are (1) to determine the capability of human brain cytochromes P-450 to metabolize psychoactive drugs and (2) to characterize and localize the multiple forms of these enzymes in the human brain. The novel hypothesis is that metabolism in specific brain regions may play an important role in modulating the therapeutic action of drugs used in the treatment of mental illness, at their primary sites of action in the brain. Understanding how the human brain metabolizes psychoactive drugs is expected to have a significant effect on the development of drugs used to treat mental illnesses such as depression, obsessive–compulsive disorder, schizophrenia, and anxiety disorders. The psychoactive drugs being studied include fluoxetine (Prozac); haloperidol (Haldol); clomipramine (Anafranil); and diazepam (Valium).

In work supported by NIMH, researchers are conducting the Prospective Neurobiological Study of PTSD (post-traumatic stress disorder). The major objectives of this ongoing research are (1) to obtain sequential measures of the activities of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS) in a large sample of psychologically traumatized persons, in the immediate aftermath of the traumatic event and in follow-up; (2) to evaluate the time course of HPA and SNS response patterns in relation to the development of PTSD; and (3) to examine possible interactions between SNS and the HPA axis in the pathogenesis of PTSD.

HPA and SNS measures will be obtained in 300 patients shortly after presentation in the emergency department at Hadassah-Hebrew University Medical Center, Jerusalem (a major urban teaching hospital), after an acute psychologically traumatic event (e.g., military or civilian war-related trauma, terrorist acts, and the entire spectrum of civilian trauma) and at specified intervals during the next 4 months. Measures of the HPA axis will include (a) levels of cortisol, adrenocorticotropic hormone, and lymphocyte glucocorticoid receptor in saliva, blood, urine, or all of or some of the three bodily fluids; (b) differences in the peak and trough of salivary cortisol levels, area under the curve, and rate of decline over the diurnal cycle; and (c) percentage of suppression of cortisol and glucocorticoid receptor induced by a 0.5-mg dose of the synthetic steroid dexamethasone. SNS measures will include (a) heart rate and blood pressure and (b) levels of norepinephrine, epinephrine, and 3-methoxy-4-hydroxy-phenylgylcol measured in saliva, blood, urine, or all of or some of the three bodily fluids.

Investigation of the Social and Cultural Dynamics of Disaster Recovery is an extension of research into the social and cultural dynamics of recovery from disaster. The initial study examined the effects of Hurricane Andrew in a sample composed equally of Latinos, non-Hispanic whites, and non-Hispanic blacks. As part of that study, a Spanish-language instrument with known psychometric properties was developed. The goal of the current project is to conduct a truly cross-cultural study by collecting post-disaster data in Mexico that can be compared with the data collected in the United States after Hurricane Andrew. Mexico provides a strikingly different cultural and economic context that will yield insights into disaster recovery in developing countries. Although the majority of disasters occur in the developing world, very little of the research has been performed there.

Two investigators at the Karolinska Institute, Stockholm, Sweden, are using positron emission tomography (PET) to study dopamine D1 and dopamine D2 receptors, respectively, in patients with schizophrenia. There has been much speculation that dopamine receptors function abnormally in patients with schizophrenia and that antipsychotic medications exert their therapeutic influence by blocking these receptors. Clinical studies have awaited the development of positron-emitting ligands for in vivo imaging of dopamine D1 and D2 receptors. Ideally, these studies should be conducted in patients with newly diagnosed schizophrenia who have therefore not been treated with antipsychotic agents. The Karolinska Institute is unique in being able to recruit such patients and in having a world-renowned research group that has developed a positron-emitting neuroreceptor ligand for use in imaging dopamine receptors.

International Meetings

An NIMH-sponsored workshop, Targeted Approaches to Suicide Prevention, was held in Bethesda, Maryland, on April 20–21, 1998. The purpose of the workshop was to review what was known about risk factors for suicide across the life course and, on the basis of available evidence, to make recommendations for prevention efforts. Nearly 50 scientists participated. International participants included a researcher from Christchurch, New Zealand, who presented findings on the risk factors for suicide attempts in young adults. A researcher from Göteborg, Sweden, reported on an autopsy study to reconstruct psychological factors that lead to suicide in late life.

The Division of Basic and Clinical Neuroscience Research, NIMH, cosponsored the 11th Genetic Analysis Workshop, in Arcachon, France, on September 8–10, 1998. At this meeting, which is a collaborative effort among genetic epidemiologists, real and computer-simulated data on topics relevant to analytic problems in genetic epidemiology are distributed to investigators from countries around the world. Almost 200 graduate students, postdoctoral students, and experienced researchers from Australia, Canada, Europe, and the United States attended the meeting.

The XVth Symposium on Brazilian Medicinal Plants was held in Aguas de Lindoia, 150 miles northwest of São Paulo, Brazil, on October 13–17, 1998. The organizing committee of the symposium invited representatives from the NIMH Extramural Program's Division of Services and Intervention Research and the NIH Office of Dietary Supplements to present research reports at the meeting. NIMH staff made two presentations: (1) The Growing Use of Medicinal Plants in the United States and (2) The Potential Psychotherapeutic Activity of Some Medicinal Plants. These reports were presented at a special symposium on the central nervous system on October 15.

Intramural Programs and Activities

The NIMH Division of Intramural Research Programs plans and administers a comprehensive long-term research program dealing with the causes, diagnosis, treatment, and prevention of mental disorders, as well as the genetic, biological, developmental, environmental, and social factors that determine human behavior and development. The Division operates laboratories and clinical branches on the NIH campus in Bethesda and at the Poolesville Animal Facilities, both in Maryland. It also maintains an independent clinical care facility at the Neuropsychiatric Research Hospital on the campus of St. Elizabeth's Hospital, Washington, D.C. Several hundred active research projects in the basic neurosciences, clinical pharmacology, clinical psychiatry, and behavioral sciences are conducted in these facilities each year. Division scientists provide a critical link between basic and applied research on mental disorders.

During FY 98, scientists in the Division of Intramural Research were engaged in a number of projects with foreign scientists. The Division offered a broad range of research opportunities for foreign scientists, including 73 Visiting Fellows, 37 Visiting Associates, and 15 Visiting Scientists from every continent except Antarctica. The investigators came from Australia, Brazil, Canada, China, England, Ethiopia, Finland, France, Germany, Hungary, India, Iran, Iraq, Ireland, Israel, Italy, Japan, Korea, the Netherlands, Poland, Russia, Spain, Sweden, and Wales.

The Division of Intramural Research Programs comprises 24 branches and laboratories. Selected examples of collaborative research projects for three branches and one laboratory are highlighted here, and the list of additional joint efforts illustrates the depth and diversity of the intramural projects.

Biological Psychiatry Branch

Development and execution of longitudinal multisite clinical trials for bipolar disorder have been significantly advanced by the collaboration among the Chief, Biological Psychiatry Branch; the Head, Stanley Foundation Bipolar Network, Bethesda, Maryland; and a scientist at the H. C. Rümke Group, Utrecht, the Netherlands. These investigators, together with other domestic researchers, have combined efforts to form a multisite clinical research network through which large numbers of patients in all phases of bipolar disorder are being evaluated by use of common research methods, protocols, and data banks. The Dutch scientist has enrolled 125 patients in Utrecht, and a total of 398 patients are enrolled in the clinical trial. For daily assessment of mood, NIMH's Life Chart Method is being used with a variety of cross-sectional rating scales.

The scientist in Utrecht has also had a key role in developing an outreach program and initiatives for children. Through an early intervention initiative, the investigators will study children and adolescents with early-onset bipolar illness, to determine whether the illness can be prevented from fully emerging or progressing. The outreach initiative expands research studies to a wide group of clinicians, so that treatment outcome can be examined in a larger cohort of patients. The scientist has developed an outreach program in the Netherlands that consists of seven clinical centers working in concert with the U.S. Bipolar Network. Initial Bipolar Network studies have identified olanzapine, lamotrigine, gabapentin, and topiramate as promising agents for treatment of bipolar disorders, and randomized controlled trials are being conducted on antidepressants (bupropion vs. sertraline vs. venlafaxine) and omega-3 fatty acids (vs. placebo).

Child Psychiatry Branch

The Child Psychiatry Branch is a clinical research branch that focuses on the causes, diagnosis, and treatment of psychiatric disorders with onset in childhood. International studies are as follows:

- a project on childhood-onset obsessive–compulsive disorders and tic disorders, in which 300 children aged 10–15 years and their primary caretaker were interviewed to assess neuropsychiatric symptoms, the course and periodicity of illness, and the association of the disorder with infection (Hospital Infantil de Mexico, Mexico City);
- studies on the neurobiology of disruptive behavior disorders (Department of Human Genetics, University of Stockholm, Sweden); and
- research on childhood-onset schizophrenia (Karolinska Hospital, Stockholm).

Clinical Neuroscience Branch

The Clinical Neuroscience Branch conducts basic and clinical research on the molecular, cellular, and genetic aspects of inherited disorders involving the nervous system. The Branch maintains extensive ongoing international joint efforts in basic and clinical research with 17 institutions in 12 countries. Four scientists conduct international research in molecular genetics, molecular neurogenetics, molecular structures, and Gaucher disease.

Molecular Genetics

In molecular genetics, collaborative studies of genetic mapping and gene isolation are being conducted at the German Cancer Research Center, Heidelberg.

Molecular Neurogenetics

In molecular neurogenetics, joint research is being performed in the following areas:

- genetic mapping of the human genome for genes responsible for psychiatric disorders, including bipolar affective disorder (Department of Human Molecular Genetics, National Public Health Institute, Helsinki, Finland);
- generation of animal models of human disease, particularly those affecting the nervous system, including infantile ceroid neurolipofuscinosis and aspartylglucosaminuria, the most common Finnish genetic disease (Department of Human Molecular Genetics, National Public Health Institute, Helsinki);
- chromosome mapping of clones having repeated trinucleotides, with use of fluorescent in situ hybridization (University of Helsinki);
- genetic mapping studies of conditions including bipolar affective disorder and other inherited disorders (Genethon, Evry, France);
- gene transfer as therapy for inherited diseases (Hôpital Robert Debré, Institut National de la Santé et de la Recherche Médicale, and Institut Pasteur, Paris, France);
- genetic studies of diseases affecting the nervous system (Department of Neurology, Brain Research Institute, Niigata, Japan); and
- electron microscope and immunopathological studies of transgenic animal models, including lysosomal diseases such as Gaucher disease (Department of Cell Biology and Genetics, Erasmus University, Rotterdam, the Netherlands).

Molecular Structures

In the study of molecular structures, collaborative research is being conducted in the following areas:

- structural studies of proteins from hibernating animals (Carleton University, Ottawa, Ontario);
- structural studies of stress proteins in plants (Botany Department, University of Toronto, Ontario);
- structural studies of *N*-hydroxylation enzymes (Chemistry Department, University of Waterloo, Ontario);
- research on crystallizing recombinant human glucocerebrosidase (University of Pierre and Marie Curie, Paris, France);
- studies on structure and function of allergens (Indian Institute of Science, Bangalore, India);
- structural studies of amyloid proteins and peptides in human disease (Heller Institute of Medical Research, Tel Hashomer, Israel); and
- studies on structure and function of neurotoxins from scorpions (Universidad Nacional Autonoma, Institute of Biotechnology, Cuernavaca, Mexico).

Gaucher Disease

In the study of Gaucher disease, collaborative research is being performed in the following areas:

- neonatal Gaucher disease (The Adelaide Children's Hospital, North Adelaide, South Australia);
- epidermal manifestations of glucocerebrosidase deficiency (Department of Dermatology, University of Erlangen, Germany);
- unusual manifestations of Gaucher disease (Gaucher Clinic, Department of Medicine, Shaare Zedek Medical Center, Jerusalem, Israel);
- unusual presentations of type 3 Gaucher disease (Department of Medical Genetics, Ajou University School of Medicine, Suwon, Korea);
- a prenatal lethal form of Gaucher disease (Department of Clinical Genetics, Erasmus University, Rotterdam, the Netherlands); and
- Gaucher disease and hydrops fetalis (Division of Medical Genetics, University of Geneva, Faculty of Medicine, Switzerland).

Laboratory of Brain and Cognition

The Section on Clinical and Experimental Neuropsychology, of the Laboratory of Brain and Cognition, conducts research (a) on factors in the central nervous system that underlie normal and abnormal behavioral states and (b) on the interaction between environmental and genetic effects on neuropsychiatric disorders including schizophrenia. Scientists in Canada, Denmark, Ecuador, and Israel are cooperating in this effort. Collaborative efforts include the following research:

- a large-scale investigation of familial genetic influences on attentional cognitive behavior in persons with absence epilepsy and schizophrenia (Montreal Neurological Institute);
- studies of occurrence of mental illness in the biological and adoptive families of Danish adoptees from a national register of 15,000 adoptees (University of Copenhagen, Denmark);
- assessment of attentional cognitive skills in a group of malnourished children, most of whom are infested with intestinal parasites, including parasitic infection of the brain—Neurocysticercosis and Performance on Neuropsychological Tests: a Family Study (Loma Linda University, Ecuador); and
- a long-term, 25-year follow-up study of children who have parents with schizophrenia and of children who have healthy parents and who were reared in a town or kibbutz in Israel (Hebrew University, Jerusalem, and Oranim Institute for Research on Kibbutz Education, Haifa University).

Other Studies

During FY 98, many other NIMH intramural collaborative research projects provided benefits to both U.S. and foreign scientists and yielded scientific information of significance and merit. Projects include the following:

- The Biological Psychiatry Branch collaborated with McGill University, Montreal, on the effect of impaired function of type II glucocorticoid receptor in transgenic mice; with the University of Rome, Italy, on the neurobiology of noncompetitive NMDA antagonists; with Josai University, Saitama, Japan, on apoptosis in neurons; and with the Tokyo Dental and Medical University, Japan, on receptor regulation in neurohybrid cell lines.
- The Clinical Brain Disorders Branch collaborated with McMaster University, Toronto, on magnetic resonance imaging studies of brain anatomy, and with Service Hospitalier Frédéric Joliot, Orsay, France, on discovery and development of radioligands.
- The Clinical Neurogenetics Branch collaborated with Institut National de la Santé et de la Recherche Médicale, Paris, France, on mapping of genes for schizophrenia, and with the Beersheva Mental Health Center, Israel, on scanning of mutations in candidate genes.
- The Laboratory of Brain and Cognition collaborated with the Weizmann Institute, Rehovot, Israel, on the functional anatomy of perceptual and memory systems in the primate brain, and with the Karolinska Institute, Stockholm, on studies of heredity and environment in schizophrenia.
- The Laboratory of Cell Biology collaborated with Philipps University, Marburg, Germany, on neuroendocrine secretory vesicle proteins and chemical coding of neurotransmission and on lentiviral neuropathogenesis, and with Royal Victoria Hospital, McGill University, Montreal, and Utrecht University, the Netherlands, on molecular biology of vasopressin and oxytocin receptors.
- The Laboratory of Cellular and Molecular Regulation collaborated with the University of Health Science, National Naval Medical Center, Bethesda, Maryland, on studies of the functional anatomy of the central nervous system and of the regulation of neurotransmission by receptors and transporters; with the Weizmann Institute, Rehovot, Israel, on the structure and assembly of the acetylcholine receptor; and with the University of Santander, Spain, on the regulation of neurotransmission by receptors and transporters.
- The Laboratory of Cerebral Metabolism collaborated with the PET Center, Hospital San Raffaele, Milan, Italy, on the kinetic modeling of tissue heterogeneity in studies of metabolism and blood flow, and with the University of Rome, Italy, on studies of protein synthesis and amino acid compartmentalization.
- The Laboratory of Clinical Science, Clinical Neuropharmacology Section, collaborated with the University of Würzburg, Germany, on animal models for the study of neuropharmacological effects and psychobiology and treatment of obsessive–compulsive disorder in adults, and with the Department of Psychiatry, Soroka Medical Center, Israel, and the Department of Human Genetics, St. Radboud Hospital, Amsterdam, the Netherlands, on the neuropharmacology of neurotransmitter and neuroendocrine regulatory mechanisms.
- The Laboratory of Clinical Science, Section on Histopharmacology, collaborated with Istituto di Anatomia Umana Normale, University of Naples, Italy, on the coexistence of peptides and neurotransmitters and calretinin.
- The Laboratory of Clinical Science, Section on Pharmacology, collaborated with the University Bern, Switzerland, on the role of neuropeptides and biogenic amines in neuroendocrine regulation of brain angiotensin receptor subtypes.
- The Laboratory of General and Comparative Biochemistry collaborated with Uppsala Biomedical Center, Sweden, on characteristics and regulation of *S*-adenosylhomocysteine hydrolase.
- The Laboratory of Molecular Biology, Unit on Neurobiology, collaborated with the Department of General Physiology, Univer-

sity of Naples, Italy, on the compartmentalization of gene expression in the nervous system.

- The Laboratory of Neurochemistry collaborated with the Oasi Institute for Research on Mental Retardation and Brain Aging, Troina, Sicily, Italy, on phenylketonuria and other diseases caused by defects in biopterin-dependent enzymes.
- The Laboratory of Neuropsychology collaborated with Oxford University, England, on neural mechanisms of stimulus memory and habit formation.
- The Laboratory of Socio-Environmental Studies collaborated with the Centre Régional de Médicine Traditionnelle, Bandiagara, Mali, in research on the migration for work and on mental health and AIDS in Mali.

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National Institute of Neurological Disorders and Stroke

INTRODUCTION

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disorders by supporting and conducting research on the normal and diseased nervous system.

NINDS collaborates with leading scientists in medical institutions worldwide to conduct, foster, coordinate, and guide research on the causes, prevention, diagnosis, and treatment of neurological disorders and stroke. The Institute also supports basic research in related scientific areas. In addition, NINDS provides grants-in-aid to public and private institutions and individuals in fields related to its areas of interest, including research project, program project, and research center grants; provides individual and institutional fellowships to increase scientific expertise in neurological fields; and conducts a diversified program of intramural and collaborative research in its own laboratories and branches. International collaboration leads to new discoveries that enable NINDS to benefit from the research of other institutions and investigators around the world. International collaboration exists in many areas, including the following:

- research involving multinational organizations;
- research grants and fellowships to foreign institutions;
- international conferences, seminars, meetings, and workshops;
- research conducted as part of the World Health Organization (WHO) collaborating centers;
- research projects uniting NINDS scientists and foreign colleagues; and
- research projects conducted by visiting scientists from all over the world.

International collaboration frequently allows scientists to conduct research that is not possible in the United States, such as studies focusing on outbreaks of neurological diseases or on geographic differences in disease distribution. For example, scientists can seek out and study extended families affected by neurological diseases with a genetic link. NINDS scientists continue to cooperate internationally to advance research and training in the neurological sciences.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Discovery of Gene for Two Types of Muscular Dystrophy

An international research effort supported by NINDS has yielded the discovery of a gene that, when mutated, causes two types of muscular dystrophy. The gene, found on chromosome 2, codes for a newly discovered protein called dysferlin, which is produced by skeletal muscles. Mutant dysferlin was seen in several families in which members had either Miyoshi myopathy, a very rare muscle disorder, or one form of limb-girdle muscular dystrophy, a more common condition. Dysferlin may be involved in maintaining the membranes of structures within cells that perform functions critical to cellular activity. Included in the research team were investigators from the Research Institute, Montreal General Hospital, Quebec; Hôpital de la Salpêtrière, Paris, France; the University of Padua, Italy; the National Institute of Neuroscience, Tokyo, Japan; King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; Hospital Sant Pau, Barcelona, Spain; and La Rabta, Tunis, Tunisia.

Neural Stem and Progenitor Cells in Adult Brain: Strategy for Repair

One of the reasons there is little recovery from damage to the central nervous system resides in the inability of the adult brain to replace neurons lost to injury or disease. The degree of recovery that is possible arises from synaptic and functional plasticity rather than the restoration of lost neurons. In recent studies, several NINDS grantees collaborated with scientists from Osaka University, Japan; the Institute of Biomedical Investigation, Mexico City, Mexico; and the University of Valencia, Spain. The research team demonstrated the presence of neuronal precursors within the subventricular zone in the brains of adult birds, rodents, and humans. In vivo, these precursors produce neurons that are recruited to restricted regions, such as the avian neostriatum and the mammalian olfactory bulb. Neural stem cells, which are the self-renewing precursors of neurons and glia, have been isolated from the central nervous systems of embryonic, adult, and aged mammals and have been maintained in culture for months. Although the size of the pool of precursor cells is minimally reduced with age, explants of these cells, taken from hosts of different ages, display identical properties and responsiveness to neurotrophic factors. Thus, neuronal precursors in the brain persist into senescence. Understanding the potential of these neurogenic cells, both in vivo and in vitro, will be critical in determining how best to use them to meet the challenge of repairing the damaged nervous system.

New Clues About Fatal Childhood Disease, Ataxia-Telangiectasia

For the first time, scientists have shown conclusively how the protein that is missing or altered in the fatal childhood disease ataxia-telangiectasia (AT) acts as a key regulator of cell division after DNA damage. The finding helps researchers to understand how cells form tumors in patients with AT, and it may lead to new understanding of other neurological and immune disorders. The new research shows that the ATM (AT mutated) protein is a protein kinase that reacts to DNA damage by chemically modifying and triggering accumulation of a molecular "brake," p53 protein. This tumor-suppressor protein, which is the master control switch for a process that normally prevents cells from dividing, is defective in about one-half of all human cancers. In patients with AT, the ATM protein is missing or defective. Consequently, the accumulation of p53 is delayed, allowing cells to replicate without repair of DNA and thereby increasing the risk of cancer. The ATM gene was isolated in 1995 at Tel Aviv University, Israel, with collaboration from an international team partially supported by NINDS. Until now, however, researchers have been uncertain about precisely how the protein produced by this gene works. The new finding was reported by the investigator from Tel Aviv University, who continues to receive support from NINDS. Now that scientists better understand how the ATM protein works, they can move toward the next stage of research—designing new treatments for AT and possibly for cancer and other disorders.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Russia

Collaboration continues with investigators from the Sakha Republic of Russia in research on Viliuisk encephalomyelitis in the Iakut people of Siberia. This disease is a progressive neurological disorder with a fatal outcome and is seen only among the Iakuts. The project has involved training of several Russian researchers in NINDS laboratories, as well as onsite data collection and evaluation in Siberia.

Activities With International and Multinational Organizations

NINDS serves as 1 of the 12 WHO Collaborating Centers for Research and Training in the Neurosciences. These centers, strategically positioned around the world, encourage scientists to investigate neurological disorders and to develop the basis for community prevention and treatment programs. Among the areas of interest are stroke, epilepsy, degenerative disorders, epidemiology of neurological disorders, and neurological disorders related to developmental problems in childhood. Each WHO center functions independently, supplying technical assistance, scientific expertise, and opportunities for collaborative research and training. Centers exchange scientific information by sponsoring conferences, workshops, and symposia and by publishing the resulting proceedings.

NINDS and WHO also cooperate in an effort to increase the ranks of qualified neurological scientists willing to undertake highly skilled investigations in more isolated, less developed regions. The International Neurological Science Fellowship Program brings investigators from developing countries to the United States for advanced research training. These scientists then return to their own countries to pursue leadership positions in neurological research and education. In fiscal year 1998 (FY 98), NINDS supported three neurological science fellowships to applicants from China, Georgia, and Russia.

Extramural Programs

NINDS supported 19 foreign research and training awards in five countries during FY 98. Additionally, numerous NINDS grants to domestic institutions incorporate foreign components. A wide range of neurological issues is being addressed, including the search for answers to key questions about the causes of neurological disorders, studies of prevention methods and potential therapies for neurological diseases, and research to identify various genes.

Clinical Trials

The NINDS Division of Stroke and Trauma, in collaboration with researchers from Canada and the United States, has provided support for studies leading to advances in clinical research on stroke. Strokes may be precipitated when narrowing of the carotid arteries in the neck reduces blood supply to the brain. NINDS supports the North American Symptomatic Carotid Endarterectomy Trial, a major clinical trial. The study has already shown that the risk for recurrent stroke is dramatically reduced by surgical clearance of the neck arteries in patients who have severe blockage due to atherosclerosis and who have already experienced signs of stroke. Further work is being done to determine whether moderate blockage warrants surgery.

The Epilepsy Therapeutics Research Program, Epilepsy Branch, conducts a multidisciplinary research effort within the extramural program of NINDS. The aim of the Program is to apply the latest findings of neuroscience research to the evaluation and development of therapies for seizure disorders. This Program, in collaboration with academic and industrial researchers worldwide, also fosters, guides, and conducts clinical studies to evaluate interventions for the prevention and treatment of seizure disorders.

International Meetings

NINDS staff continue to undertake various initiatives to establish new ties and share research information and strategies with their international colleagues. This collaborative effort facilitates pooling information and ideas, accelerates ongoing projects, and promotes interest in medical problems needing greater attention.

In October 1997, NINDS and the International Federation of Multiple Sclerosis Societies cosponsored the Workshop of the Genetics of Multiple Sclerosis, held in Madrid, Spain.

Other international conferences and workshops attended by NINDS staff include:

- Xth World Federation of Neurology International Congress on Neuromuscular Diseases, in Adelaide, Australia;
- International Society of Magnetic Resonance, in Sydney, Australia;
- International Symposium: Immunopathology of Multiple Sclerosis, in Vienna, Austria;
- 7th Annual Meeting of the European CMT (Charcot-Marie Tooth) Consortium Group, in Antwerp, Belgium;
- Symposium on Molecular Mechanisms of Synaptic Plasticity, at Istituto de Ciencias Basicas da Saude, in Pôrto Alegre, Brazil;
- 3rd International Workshop on Molecular Epidemiology and Evolutionary Genetics of Infectious Diseases, in Rio de Janeiro, Brazil;
- 12th Biennial Meeting of the International Society for Developmental Neuroscience, in Vancouver, British Columbia;
- 4th Annual Conference on Functional Mapping of the Human Gene, in Montreal, Quebec;
- 5th Congress of the International Society on Neuroimmunology, in Montreal;
- Meeting of the North American Stroke Association, in Montreal;
- Gordon Conference on Molecular and Cellular Neurobiology, in Beijing, China;
- Symposium on Cell and Gene Therapy in Parkinson's Disease and Other Neurolog-

ical Disorders, in Beijing;

- 6th Pacific Rim Biotechnology Conference, in Hong Kong, China;
- 10th African Conference in STD/AIDS (sexually transmitted disease and acquired immunodeficiency syndrome) in Africa, in Abidjan, Côte d'Ivoire;
- 23rd International Herpesvirus Workshop, in York, England;
- 11th European College of Neuropsychopharmacology, in Paris, France;
- 3rd Congress of the European Association for Neuro-Oncology, in Paris;
- Dopamine '98, in Strasbourg, France;
- International Workshop on Dyskinesia Assessment, in Toulouse, France;
- 70th Annual Meeting of the German Society for Neurology, in Dresden, Germany;
- XIIIth Congress of the European Society for Stereotactic and Functional Neurosurgery, in Freiberg, Germany;
- 49th Annual Meeting of the German Society of Neurosurgery, in Hannover, Germany;
- 7th International Symposium on Pharmacology of Cerebral Ischemia, in Marburg, Germany;
- XIIIth International Congress of Pharmacology, in Munich, Germany;
- European Meeting on Glial Cell Function in Health and Disease, in Athens, Greece;
- 18th European Workshop on Rheumatology Research, in Athens;
- 7th International Conference on Peripheral Dopamine, in Dublin, Ireland;
- 4th Eilat Conference on New Antiepileptic Drugs, in Tel Aviv, Israel;
- Annual Meeting of the Italian Association of Neuroradiology, in Cosenza, Calabria, Italy;
- 2nd International Symposium on Therapeutic Strategies in Ischemic Stroke, in Genoa, Italy;
- VIth International Symposium on Mechanisms of Secondary Brain Damage—Novel Developments, in Mauls, Italy;
- 3rd International Workshop on Maturation Phenomenon in Cerebral Ischemia, in Pozzilli, Italy;
- 13th International Conference on Comparative Physiology, in Troina, Sicily, Italy;
- 2nd International Symposium on Treatment of Parkinson's Disease, in Kobe, Japan;
- 39th Annual Congress of the Japanese Society of Neurology, in Kyoto, Japan;
- 6th International Evoked Potentials Symposium, in Okazaki, Japan;
- International Symposium on the Cardiovascular System and Signal Transduction, in Osaka, Japan;
- 4th Japan Society Meeting on Lipidosis, in Tokyo, Japan;
- 5th Annual Epilepsy Symposium, in Seoul, Korea;
- 6th International Conference on Alzheimer's Disease, in Amsterdam, the Netherlands;
- 17th Scientific Meeting of the International Society of Hypertension, in Amsterdam;
- 30th Anniversary of the Polish Academy of Sciences, in Warsaw;
- European Stroke Meeting, in Edinburgh, Scotland;
- 8th International Child Neurology Congress, in Ljubljana, Slovenia;
- VIIIth Meeting of the Spanish Infectious Diseases Society, in Mallorca, Spain;
- 3rd Congress of the Euroacademy for Multidisciplinary Neurotraumatology, in Zürich, Switzerland; and
- PAHO (Pan American Health Organization)-WHO Collaborating Centers Conference, in Washington, D.C.

Intramural Programs and Activities

The NINDS Division of Intramural Research consists of 11 branches and 11 laboratories. Many of the scientists in the Division engage in international research through collaboration with foreign scientists and through assignments in laboratories in other countries.

Biometry and Field Studies Branch

A scientist in the Biometry and Field Studies Branch continues to collaborate on several epidemiologic studies with investigators from the Foundation for Neuroepidemiologic Research, Junín, Argentina; the School of Medicine, University of Chile, Santiago; the Institute of Hygiene, University of Padua, Italy; the School of Medicine, Erasmus University, Rotterdam, the Netherlands; and University Hospital, "12th of October," Spain. The studies include prevalence surveys on major neurological disorders; a case–control study on alcohol consumption and hemorrhagic stroke; a field study to obtain normative values for the Mini–Mental State Examination in a healthy population; and a study of methods to verify cases of Parkinson's disease, which can affect estimates of the prevalence of this condition. The study of methods for case ascertainment underscored the difficulties in making meaningful comparisons of prevalence estimates when diagnostic criteria differ among studies or when the numbers of study participants vary greatly across age groups.

Developmental and Metabolic Neurology Branch

The Developmental and Metabolic Neurology Branch maintains major international collaborations with investigators at Hôpital St. Vincent de Paul, Paris, and Clermont-Ferrand University, France, who are studying genetic aspects of leukodystrophies. Joint efforts with investigators from Panum Institute, Copenhagen, Denmark, and Marseille University, France, are focusing on the genetic aspects of and enzyme replacement therapy for Fabry's disease. Scientists in the Branch also are collaborating with a research team at Tottori University, Yonago, Japan, to identify a second gene that is mutated in patients with type C Niemann-Pick disease. Mutations in this gene produce a clinical phenotype identical to that caused by a mutation in the NPC1 gene that Branch scientists identified and cloned in FY 97. This study is particularly important because it indicates that an uncharacterized protein, coded by a gene that is not on chromosome 18 where the NPC1 gene is located, can cause a disease that is clinically similar to the disease caused by the NPC1 gene.

Experimental Therapeutics Branch

In the Experimental Therapeutics Branch, Clinical Pharmacology Section, Visiting Scientists from Canada, China, England, Greece, and the Netherlands participated in studies of the pathogenesis and treatment of Parkinson's disease. This work has made use of primate animal models to investigate the role of oxidative stress and toxicity induced by overexcited neurons in causing the degeneration of dopamine-producing nerve cells. Findings may show that functional repair can result from treatment with certain neurotrophic factors. A Visiting Scientist from Japan studied apoptotic (cell suicide) mechanisms in selected brain cells. He found that a novel scavenger of free radicals protects striatal neurons from cell death in a model of Huntington's disease. Joint research projects with scientists at the University of Barcelona, Spain, and the University of Göteborg, Sweden, are continuing.

Investigators in the Branch's Genetic Pharmacology Unit continue to work with scientists at the Institute of Brain Research, University of Tokyo, Japan, in a search for interactions between transcription factors and cofactors and for the relevance of these interactions to certain neurodegenerative diseases. Special Volunteers from China and England are investigating gene regulation of dopamine receptors. A Special Volunteer from Japan recently joined the research group to study cellular models of neurodegeneration. In addition, a Visiting Scientist from Germany recently completed an investigation of the effects of steroid hormones on dopaminergic neurotransmission in the brain, and three Visiting Scientists from Korea continue to focus on transcriptional control mechanisms and gene transfer in the brain.

Researchers in the Neurophysiological Pharmacology Section are continuing joint efforts with a scientist in the Department of Integrative Physiology, National Institute for Physiological Sciences, Myodaiji, Okazaki, Japan. The goal of these studies is to develop mechanisms to quantitate the properties of the slow oscillations in electrical activity in the basal ganglia recently described by scientists in the Section.

Medical Neurology Branch

Scientists from the NINDS intramural Medical Neurology Branch (MNB) are working with the Rehabilitation Institute of Castel Goffredo, Salvatore Maugeri Foundation, Istituto di Ricovero e Cura a Carattere Scientific, Italy. The research is being conducted in three main areas: (1) formulation of guidelines on acquisition of data on electromyogram signals; (2) research on magnetic stimulation of the peripheral nerves and the cortex; and (3) development of a new technique to determine the membrane time constant of a peripheral nerve. Also, the Branch consults and exchanges visits with scientists from Istituto Nazionale a Carattere Scientific, Florence, Italy, on studies of balance control in older adults. Techniques are being developed to screen large numbers of subjects by evaluating objective measurements of standing balance. The general goal is to understand the contribution of different pathological conditions to falls in older adults. Scientists from Austria, Colombia, France, Germany, Italy, Japan, Switzerland, and Turkey have worked in the laboratory.

A senior scientist from MNB is participating in a number of joint research projects with investigators from Fukui Medical School and the University of Kyoto, Japan, on electrophysical and neuroimaging analysis of motor control. He has also attended meetings in Belgium, France, Germany, Italy, and Japan.

The Neuromuscular Diseases Section, MNB, has established a joint study with the University of Athens Medical School, Greece, to explore the mechanism of nerve injury in patients with vasculitis and Sjögren's syndrome. Also, the Section collaborates with the Department of Pediatrics at the medical school in performing linkage studies in families with recurrent paralysis of the facial nerve (Bell's palsy). This is an important study because Bell's palsy is a common problem throughout the world, particularly in certain regions in Greece where it occurs in many people in the same village. The Chief of the Section also consults with the Neurology Department to establish new therapeutic protocols for patients with specific demyelinating neuropathies and types of multiple sclerosis prevalent in Greece. The Section has maintained a joint study in Mongolia, in an attempt to find genes responsible for a hereditary motor neuron disease that is prevalent there. In addition, the Section has two Visiting Scientists from Japan and Korea who are trained in the immunology of muscle disorders. They have made significant strides in identifying important molecules in muscle that regulate the immune response; they plan to return to their own countries to set up similar laboratories and establish joint studies.

The goal of the Human Cortical Physiology Section, MNB, is to understand the mechanisms underlying plastic changes in the human central nervous system and to develop novel therapeutic approaches for recovery of function, on the basis of these advances. Joint research projects have been initiated or are continuing at the University of Buenos Aires, Argentina, to study changes in the motor cortex of stroke patients, by using transcranial magnetic stimulation, and at Humboldt University, Berlin, Germany, to investigate plastic changes in the motor and somatosensory cortex of amputees with phantom limb pain, by using transcranial magnetic stimulation and magnetoencephalography. Coordinated research with scientists from the Department of Biomedical Imaging Research Center, Fukui Medical School, Japan, has shown that, in blind subjects, the ability of the brain to compensate by developing senses other than vision (cross-modal plasticity) does not occur when vision is lost after 14 years of age. The Section also hosted Visiting Scientists and Special Volunteers from Germany and Italy in its laboratory.

Investigators from the Cognitive Neuroscience Section, MNB, are studying the functions of the prefrontal cortex of the human brain with scientists from Cognitive Science Institute, Lyon, France; the University of Modena Clinical Center and the University of Pisa, Italy; the University of Barcelona, Spain; and the Neurology Department, Hospital de Galdakao, Spain. In particular, the scientists are focusing on the role of the prefrontal cortex in regulating mechanisms for reward and punishment, in modulating aggressive human behavior, and in the processing of timing and order of events. The Section is hosting Visiting Scientists from Bulgaria, Canada, France, Israel, and Italy. These scientists are performing research in diverse areas related to cognition, including reasoning, planning, time perception, aggression, attention, mathematics, memory, and neuroplasticity.

Scientists from the Clinical Neurogenetics Unit, MNB, are working with scientists at the China-Japan Hospital, Beijing, China, and the Mongolian and Sakha (Russia) Institutes of Health, to identify molecular mechanisms involved in human neurodegenerative disorders prevalent in Asian populations of China, Mongolia, Russian Siberia, and Thailand. One of the scientists in the Clinical Neurogenetics Unit is an appointed WHO expert. He is helping to establish a program of extensive studies on clinical and neuropathological characterization and epidemiology of Viliuisk encephalomyelitis, an emerging contagious disease in Russian Siberia. In FY 98, the scientist spent 1 month in Siberia for onsite studies of the epidemic of this contagious fatal disorder that has recently spread an additional 600 miles from its original focus. A program of further studies of the disease has been developed and approved by WHO. The program includes clinical criteria for diagnosis and rules for surveillance, as well as attempts to isolate the causative agent and analysis of mechanisms of disease transmission within families and villages, to prevent further spread through human migration.

Neuroepidemiology Branch

A geneticist from the University of Western Australia, Perth, has been working with scientists in the Neuroepidemiology Branch on the International Collaborative Study of Childhood Neurologic Morbidity in Multiple Births. The scientists collected data from population-based studies in Australia, England, Sweden, and the United States. These data, containing information on 1.2 million births, are being examined to determine the relationship between the birth of twins and neurological disability or mortality, as well as the mechanisms involved.

Stroke Branch

The Stroke Branch hosts in its laboratories scientists from various countries including China, Germany, and Japan. These scientists are investigating the mechanisms responsible for development of tolerance to ischemia in animal models and tissue culture; the effects of leukocytes, tumor necrosis factor α, and other mediators of inflammation on microcirculatory perfusion during acute brain ischemia in spontaneously hypertensive rats; the development of a "regulatable" transgenic mouse model that will allow certain genes to be switched on or off; and measures to prevent stroke in stroke-prone rats.

Laboratory of Central Nervous System Studies

The Laboratory of Central Nervous System Studies (LCNSS) functions as a consultant group to the Creutzfeldt-Jakob Disease (CJD) Surveillance Unit at the Western General Hospital and the Neuropathogenesis Unit of the Medical Research Council, both associated with the University of Edinburgh, Scotland. This Unit oversees the European CJD surveillance program, helping to achieve an optimal method for epidemiologic studies, which continue to provide crucial background data on the current CJD outbreak in the United Kingdom. The outbreak is thought to be related to bovine spongiform encephalopathy (BSE; "mad cow" disease).

Other joint research, with personnel from the University of Melbourne and Royal Perth Hospital, involves identification of causative mutations and study of blood infectivity in Australian families with other prion diseases.

Experts from LCNSS have served as epidemiologic consultants to the European Community BioMed 2 CJD Surveillance Group and as consultants on the clinical and genetic aspects of CJD to the European Community BioMed 2 Prion Disease Neuropathology Group.

LCNSS staff and investigators from the University of Montpellier, France, are participating in a joint study of natural and experimental oral infection of lemurs with BSE, to determine the timed appearance of infectivity in various organs of the body during the course of infection.

Investigators from LCNSS are collaborating with the Institute of Psychiatry and Neurology, Budapest, Hungary, in a study of a unique family with Gerstmann-Sträussler-Scheinker (GSS) disease, a rare familial prion disease, in which three sisters died of conditions with features of GSS, CJD, and Alzheimer's disease.

Laboratory of Molecular Biology

The Laboratory of Molecular Biology maintains close ties with the Center for Genome Research, University of Edinburgh, Scotland. The Chief of the Laboratory has organized international meetings in collaboration with investigators at the Center for Genome Research.

Laboratory of Neural Control

The Laboratory of Neural Control is collaborating with scientists in several countries on research in spinal cord structure and function. In one joint project, scientists at the Laboratory and at the University of Bristol, England, are exploring the mechanisms by which respiratory rhythms are produced in the brain stem. The genesis and control of rhythmic movements by the central nervous system is a key area of research. This research holds great promise for increasing understanding of problems such as sudden infant death syndrome and for improving the prognosis for patients with spinal cord injury.

In another cooperative effort, a scientist at the University of Newcastle upon Tyne, England, is collaborating in a study of the mechanisms that produce spontaneous waves of activity in neurons in the retina of the chick embryo. These waves are thought to be critical for the formation of proper connections between retinal nerve cells.

Collaboration continues with scientists at the University of Paris, France, on examination of the role of intrinsic cellular properties in the production of rhythmic movements such as locomotion in the isolated spinal cord in the chick. Scientists in the Laboratory are also collaborating with colleagues at the Hebrew University Medical School, Jerusalem, Israel, on the development of connections between the motor cortex in the rat brain and targets in the spinal cord. Because the central nervous system in the rodent has become a major model system for neuroscience research, there is a great need to study its structure and function. This work will be supported in part by the U.S.-Israel Binational Science Foundation, which is a key source of financial support for collaborative research with Israeli scientists. In addition, the Laboratory is hosting investigators from Canada, China, France, and Ukraine in the Postdoctoral Fellowship Program.

These technically difficult study areas have involved and will continue to require international cooperation and collaboration, to the benefit of all the countries involved.

NIH Visiting Program

In summary, during FY 98, the NINDS Division of Intramural Research hosted 18 Visiting Scientists, 36 Visiting Associates, and 52 Visiting Fellows.

XXI.
National Institute of Nursing Research

INTRODUCTION

The National Institute of Nursing Research (NINR) was established at the National Institutes of Health in 1986. According to its broad mandate, the Institute blends behavioral and biomedical research to

- understand and ease the symptoms of acute and chronic illness;
- prevent or delay the onset of disease or disability or slow its progression;
- find effective approaches to achieving and sustaining good health; and
- improve clinical settings in which care is provided.

NINR's research extends to problems encountered by patients, families, and caregivers. It also emphasizes the special needs of underserved populations, including those at risk of poor health. These efforts are critical for translation of scientific advances into cost-effective health care that does not compromise quality.

NINR accomplishes its mission by supporting grants to universities and other research organizations, as well as by conducting intramural research at laboratories in Bethesda, Maryland. The research fosters multidisciplinary collaborative work to ensure a comprehensive approach to the study of illness and disabling conditions. This approach is especially relevant in research on

- long-term care for older adults;
- the special needs of women across the life span;
- optimum care at the end of life;
- issues related to genetic testing and counseling;
- management of prevention and treatment of infectious diseases; and
- environmental influences on risk factors related to chronic illnesses.

NINR's intramural investigations have a multidisciplinary patient-focused approach to human health and illness. Questions addressed in the research are related to patient care and quality of life, for example, (a) the management of chronic wounds that often accompany periods of long-term illness and immobility and (b) the pathogenesis underlying delayed healing of these wounds.

In addition, the Institute supports comprehensive research training programs to prepare individuals with requisite interdisciplinary skills to conduct nursing research.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Extramural Programs

Grants

An NINR-supported grantee is conducting field research in Matlab, Bangladesh, on a public health intervention to prevent or reduce the incidence of cholera in areas where people must depend on natural groundwater after natural disasters such as flooding. The research involves a simple filtration method that uses widely available sari cloth to filter household water. The intervention is based on earlier studies that found sari cloth effective in reducing the number of plankton associated with *Vibrio cholerae* in surface water to below the infectious level that causes cholera. Investigators are evaluating the effective use of the technique by villagers, including whether the number of *V. cholerae* cells in water and the incidence of cholera are reduced.

Another NINR grant involves a 10-site, randomized control study in Canada and the United States. The research is designed to reduce the unacceptably high rates of birth by cesarean section in these two countries. Earlier studies conducted on a smaller scale showed that the amount of "labor support" by caregivers during active labor can influence cesarean delivery rates and other adverse events related to childbirth. The elements of labor support being studied include companionship, attention to emotional needs, and comfort. The researchers are evaluating the results of two types of nursing care on women in labor—continuous support and the usual intermittent nursing care. They are comparing the effects of these types of care on rates of cesarean delivery and forceps delivery and requirements for pain reduction, particularly for administration of epidural anesthesia. Cost-effectiveness is also being addressed. The findings will contribute knowledge about the effectiveness of labor support for a variety of events related to childbirth, such as prolonged hospital stay and postpartum depression. The results of this study are expected to inform policy decisions about the staffing of hospital delivery suites.

A research project supported by NINR addresses hospital restructuring, which is widespread in Europe and the United States. The study provides the opportunity to evaluate restructuring modifications and recommend changes to improve health care for hospitalized patients. There is little scientific evidence on the best approaches to restructuring hospitals or the effect of specific approaches on outcome for patients. This research involves hospitals in Canada, England, Scotland, and the United States, which are in different stages of restructuring. Investigators are evaluating the effects of organizational changes, including variations in nurse staffing, on patient outcomes. Also under study are the effects of nurses' personal control over nursing practice and their relationships with physicians. The investigators are also analyzing hospital mortality rates, complication rates, and rates of unsuccessful resuscitation, as well as organizational barriers to timely use of critical clinical interventions.

NINR funds U.S. training fellowships for three predoctoral students who are performing dissertation research in Nicaragua and Peru. The trainees are undertaking studies on the relationship between the women's movement and women's health in Nicaragua; understanding and management of cancer in Peruvian Amazonia; and improving infant nutrition in Trujillo, Peru.

International Meetings

NINR staff participated in the meeting of the International HIV (human immunodeficiency virus) Nursing Research Network, in London, England. The network participants meet twice a year to collaborate on international research on the care of patients with HIV.

NINR also hosted a Visiting Scholar, who is the Chair of Acute Care Nursing at Cabrini Hospital, Deakin University, Victoria, Australia. She was briefed about U.S. nursing research on patient outcomes and about enhancing the educational and research activities of her institution.

XXII.
National Library of Medicine

INTRODUCTION

The year 1998 saw continuing leadership by the National Library of Medicine (NLM) in several areas of international work:

- furthering of global Internet connectivity;
- provision of Internet connectivity and access to information for malaria researchers in Africa;
- approval of the report of the Long-Range Planning Panel on International Programs by the NLM Board of Regents; and
- planning of the first meeting for implementation of the panel's report.

Internet communications connectivity and access to information resources by malaria research scientists in Africa is part of the Multilateral Initiative on Malaria—a major initiative undertaken by NLM in collaboration with the National Institute of Allergy and Infectious Diseases, the Fogarty International Center, and the Office of the Director, National Institutes of Health (NIH).

Other international activities were carried out with individual countries and governmental and nongovernmental organizations. Information management training was provided to colleagues from abroad, numerous professional visitors were received from around the world, and publications were exchanged with libraries in other countries.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

NLM Long-Range Planning Panel on International Programs

The NLM Long-Range Planning Panel on International Programs was chartered by the NLM Board of Regents in May 1995 to advise NLM on the relative priority of its international activities and responsibilities and to assist in the development of appropriate strategies consistent with the Library's statutory mission and available resources. The panel was chaired by former NIH Director Donald S. Fredrickson. It consisted of 25 distinguished members assisted by expert consultants in medicine, telecommunications, health sciences librarianship, electronic publishing, and related fields. The Acting Chief, Office of Planning and Analysis, served as executive secretary to the panel. This panel, which met three times in 1996–1997, made the following formal recommendations to the board on the future of NLM's international activities:

- Objective 1: Strengthen and expand global access to the world's health-related literature.
- Objective 2: Chart new routes to biomedical knowledge and its use.
- Objective 3: Enable NLM to fulfill its international mission.

As a result of Board of Regents' approval of this plan, an International Partners meeting is scheduled to be held at NLM, in Bethesda, Maryland, on December 1–2, 1998. This meeting will explore new cooperative efforts between NLM and a variety of entities in countries around the world, including the international MEDLARS Centers. These efforts mark the beginning of a new network of international partners, as envisioned in the report of the panel. Designed to showcase current NLM activities and provide a forum for ideas from the field, the meeting will focus on new collaborative activities in three areas: document delivery, enhancing connectivity and infrastructure, and the special needs of developing countries.

Internet Connectivity at Malaria Research Sites in Africa

"What a pleasure for us and our collaborators to sit in our offices and browse the Web sites, being in contact with the world in a few seconds, looking for the hidden world. What a great potential we are discovering." These words of the Director of the Malaria Research and Training Center, Bamako, Mali, reveal at once the excitement of African scientists and the potential that Internet access holds for scientific research. Since June 1998, he and his colleagues at the Center have had access to the Internet and the World Wide Web through microwave technology. The equipment (including a local network), installation, and training were funded by the National Institute of Allergy and Infectious Diseases, NLM; the Office of the Director, NIH; and the World Bank.

This story from Mali is the first chapter in the work of the Multilateral Initiative on Malaria (MIM) Communications Working Group, chaired by NLM. The major objectives of MIM are support for African scientists, the ability of malaria researchers to connect with one another and sources of information, and the creation of new collaborations and partnerships.

The initial meeting of the MIM Communications Working Group was held at NLM, in Bethesda, Maryland, in January 1998. In attendance were malaria research scientists, health information professionals, telecommunications experts, and representatives of the major agencies that fund MIM. In keeping with the goal of supporting a broad spectrum of basic and operational needs for malaria research, the investigators requested communications and connectivity capabilities sufficient to provide robust and reliable electronic mail (e-mail); links among research sites; access to the full text of journal articles; database searching; exchange of large files and mapping data; and timely access to electronic information resources worldwide.

In addition to the malaria research site in Mali, the MIM Communications Working Group endorsed five other locations for the initial connectivity phase: the site of the Centers for Disease Control and Prevention (United States) and the Kenya Medical Research Institute (KEMRI), in Kisian; the site of the Wellcome Trust (United Kingdom) and KEMRI, in Kilifi; and three sites of the

National Institute of Medical Research, in Dar es Salaam, Ifakara, and Amani, Tanzania. Several of the sites already have computer equipment and training. Most of the sites are in relatively remote locations, however, and traditional means of connecting to the Internet are not viable, because of the unreliability of telephone service or restrictions on the bandwidth of rates for data transfer.

Subsequently, NLM supported site visits and assessments, consultation, and evaluation and testing of equipment existing at the site. In drafting an implementation plan, the MIM Communications Working Group considered issues such as user training, in-country licensure of technology, and allowances for future technological advances (e.g., predicted worldwide availability of low-cost commercial satellite systems).

The plan recommends immediate use of affordable technologies to provide high-speed and reliable information and communication links. The goal is to achieve timely improvement in the ability of scientists to collaborate in research and to disseminate the findings. Recommended technologies are VSAT, which uses a geostationary satellite and a small earth station, and microwave, which uses radio waves. Microwave equipment is less expensive but is limited to line-of-sight transmission. The MIM sites that request a radio or VSAT link must gain permission from the relevant in-country authority.

With the Mali model fully operational, NLM has stepped forward with an offer to fund the initial equipment and installation costs at these five sites if partner funding organizations make a commitment to support ongoing operational costs. Sustainability is an essential ingredient for achievement of lasting connectivity at these research sites. At the site in Kisian, Kenya, a funding partnership between NLM and the Centers for Disease Control and Prevention is firmly in place. An NLM special expert is responsible for project coordination.

Global Internet Connectivity

In 1998, NLM continued and expanded the testing and evaluation of end-to-end Internet connectivity. This project is intended to explore the methods and measurements needed to better understand the quality of Internet performance from the perspective of the user. To do this, NLM is using test methods that measure, for example, the size of the Internet transmission "pipe"; the round-trip time for sending packets of information to the destination and back; the percentage of packets lost during transmission; and response time. NLM is collaborating with numerous domestic and international partners to test Internet pathways around the world.

NLM monitors about 85 network paths to hosts (typically Web servers) in 29 countries and 14 time zones. Hosts are located in all major regions of the world: sub-Saharan Africa; Central, North, and South America; East, South, and Southeast Asia; Eastern and Western Europe; and the Middle East. The monitoring includes locations in all G7 and G8 countries. NLM is conducting symmetrical (two-way) and time zone testing with three partners, as part of the G7 and G8 Internet connectivity initiative. These partners are the Western Universities Research Consortium at the University of Calgary, Alberta; OMNI (Online Medical Networked Information) at the University of Nottingham, England; and ForthNet SA, in Crete, Greece. In addition, NLM has conducted special testing of Internet pathways to sites in several sub-Saharan countries and in Mexico and Russia.

Results of phase I of the Internet connectivity project were published in an article entitled Evaluating Internet End-to-End Performance: Overview of Test Methodology and Results, in the Journal of the American Medical Informatics Association (November/December 1998).

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Activities With International and Multinational Organizations

International Council for Scientific and Technical Information

Working in collaboration with the International Council for Scientific and Technical Information, a component of the International Council of Scientific Unions, NLM helped to successfully conclude a pilot demonstration project to reduce existing technological and tariff barriers to the flow of scientific and health-related information over the Internet to developing regions of the world. Focused in the eastern Caribbean, this effort was carried out in conjunction with the United Nations Educational, Scientific, and Cultural Organization (UNESCO); the Pan American Health Organization (PAHO); the International Telecommunications Union; and the United Nations Development Programs. UNESCO published the final report, Pilot Project on Access to Telematics Facilities in the Eastern Caribbean, in 1998.

G7 Global Healthcare Applications Project

Health is one of 11 theme areas identified by President Bill Clinton and his counterparts in the G7 nations, for study to demonstrate the value of information technology in addressing societal needs. NLM is leading a project activity that is premised on the notion that many G7 Global Healthcare Applications projects depend in whole or in part on the availability of the Internet. As the preferred technical means for the exchange of biomedical information with and among the G7 nations and beyond, the Internet is a critical component of the emerging global health information infrastructure.

NLM, in conjunction with researchers from the G7 countries and other domestic and international partners, has undertaken Internet testing that should improve understanding of Internet connectivity from the user's perspective and, ultimately, help to better inform users about selecting Internet services and solving problems in use of the Internet. NLM has identified a need for objective and widely accepted methods of characterizing and diagnosing the quality and performance of Internet connections under various conditions (e.g., locations, distances, time periods, and data volumes). An important finding has emerged: local bottlenecks, rather than inadequate bandwidth on the international links, are the primary source of most congestion problems on the Internet.

Multi-Language Anatomical Digital Database

A second U.S.-led project, the Multi-Language Anatomical Digital Database, was developed by NLM. Germany, Italy, and Japan participate in this program, which takes advantage of the multilingual capabilities of the Unified Medical Language System and facilitates multilingual access to the future

Visible Human Database. The database consists of images that are inherently word free and language neutral; thus, with the addition of multilingual anatomical labeling, these images can serve multilingual needs. The project will serve as a test bed for a range of applications, including medical education, patient information, and telemedicine consultation. The multilingual capability is especially advantageous for international applications.

International Visitors

NLM continues to be a focal point for visitors of the international community from a variety of disciplines. Many of these visitors are responsible for medical, scientific, or technical information in their own countries. Visitors are officially received and briefed on relevant aspects of NLM operations and research. Among the visitors in fiscal year 1998 were representatives from Cameroon, China, Czech Republic, Germany, India, Indonesia, Israel, Japan, Kenya, Macedonia, Mali, Mexico, Nigeria, Norway, Senegal, South Africa, Sweden, Switzerland, United Kingdom, Zambia, and Zimbabwe.

XXIII.
National Center for Research Resources

INTRODUCTION

The National Center for Research Resources (NCRR) develops and supports critical research technologies and shared resources that underpin research to maintain and improve the health of the Nation's citizens. NCRR supports the development and use of sophisticated instrumentation and technology, animal models for studies of human disease, and clinical research environments, as well as the enhancement of research capacity for underrepresented groups.

International cooperation provides opportunities to achieve a wide range of research and resource objectives and offers access to biological resources available only in foreign countries. Through cooperation and collaboration with national and international organizations, NCRR plans biomedical research programs in support of National Institutes of Health activities.

NCRR sponsors international activities through four extramural components: Biomedical Technology, Clinical Research, Comparative Medicine, and Research Infrastructure.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

NCRR supports the Cambridge Crystallographic Data Centre, England, which builds and maintains the Cambridge Structural Database, the largest searchable database of crystal structures that have been determined by biomedical researchers. This database contains crystal structure information for more than 190,000 organic and metal organic compounds and is the only available file of x-ray crystallographic coordinates for compounds of low molecular weight. The Cambridge Crystallographic Data Centre distributes the database and software to more than 600 academic and commercial users worldwide.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Activities With International and Multinational Organizations

International Adoptees

Within 1 month of their arrival in the United States, 294 adopted children from Asia, the Caribbean, and Central and South America were evaluated with screening tests for hepatitis B, human immunodeficiency virus (HIV), tuberculosis, syphilis, cytomegalovirus, intestinal parasites, and anemia. All the tests were performed in the United States. The Computerized Data Management and Analysis System of the General Clinical Research Center (GCRC) at the University of Minnesota, Minneapolis, was used to analyze these data. The results indicated that the rates of hepatitis B, tuberculosis, and intestinal parasites are significantly higher in international adoptees than in children born in the United States and that the adopted child at high risk for these diseases is typically an Asian female older than 3 years of age.

International Registries

The International Fanconi Anemia Registry is a repository for clinical, hematologic, and genetic information on patients with Fanconi anemia, a rare disease. The registry was established at Rockefeller University, New York City, New York, in 1982, to collect this information and to make it available to researchers. Patients with Fanconi anemia are seen at the Rockefeller University GCRC, New York, where the registry is maintained. Active collaborative efforts continue with investigators at several centers in the United States, as well as the Hospital St. Louis, Paris, France; the University of Heidelberg, Germany; and the University of Parma, Italy.

In addition, NCRR provides support for specimen collection and biostatistics for the International Skeletal Dysplasia Registry through its GCRC at Harbor-UCLA (University of California, Los Angeles) Medical Center. Skeletal dysplasias are a heterogeneous group of disorders resulting in disproportionate short stature, skeletal deformities, or both. The data from this registry are from multidisciplinary investigations of the clinical, genetic, morphological, biochemical, and molecular characteristics of the skeletal dysplasias.

Hypertension Optimal Treatment International Study

The Hypertension Optimal Treatment International Study is being conducted in collaboration with investigators in Canada, China, England, Germany, Mexico, and Sweden. A substudy examining renal clearance is under way at 10 centers in the United States, including the GCRC at the University of Texas, Houston.

Hyperkinesia in Schizophrenia Not Treated With Neuroleptic Agents

NCRR supports a study that addresses long-standing questions about the nature and origin of hyperkinesia in schizophrenia. Investigators are studying a group of Moroccans with schizophrenia who have a long duration of illness but have never received neuroleptic medication. This group is being compared with matched groups of healthy control subjects who do not have schizophrenia and patients at the GCRC, Oregon Health Sciences University, Portland, who have schizophrenia and have received long-term treatment with neuroleptic medication.

International Trial of Viramune in AIDS

An NCRR-supported GCRC at Indiana University, Indianapolis, is participating in an international, double-blind, randomized, phase III study to evaluate agents for prevention of clinical events in progression of acquired immunodeficiency syndrome (AIDS) and for prevention of death from AIDS. The investigators are testing the tolerance, safety, and effectiveness of Viramune (nevirapine) in combination with lamivudine and stable background nucleoside therapy.

Extramural Programs

Brazil

The Wisconsin Regional Primate Research Center (RPRC), Madison, continues to support a project on the social regulation of fertility in wild, free-ranging common marmosets (*Callitrichid* spp.) near Natal. This study has involved the development of novel fecal assays for noninvasive monitoring of reproductive events in marmosets in captivity and in the wild. Before this collaboration between the Wisconsin RPRC and Universidade Federal do Rio Grande do Norte, Natal, such studies were limited to captive marmosets.

At a forested site near Minas Gerais, investigators from the Wisconsin RPRC are also conducting a research project on female fertility and reproduction in wild *Muriqui* monkeys, an endangered New World primate. In an analysis of selected reproductive events, researchers are evaluating longstanding questions about the hormonal control of sexual behavior, the suppression of ovulation by lactation, the nature and extent of adolescent sterility, and regulators of seasonal reproduction. These findings may well contribute to the survival of this species.

Canada

In fiscal year 1998, NCRR's Comparative Medicine area continued to support researchers who study the small nematode *Caenorhabditis elegans*. These researchers are developing a comprehensive genetic "tool kit" for the organism. Investigators at the University of British Columbia, Vancouver, coordinate research activity with other groups, including researchers at the University of Missouri, Columbia. The tool kit is a collection of chromosomal "balancers" covering the *C. elegans* genome. These balancers are base-pair rearrangements that suppress genetic recombination. Researchers at the University of British Columbia have completed mapping of the balancers for several chromosomes and have made strains and information available to the community of investigators studying *C. elegans*, through the *Caenorhabditis* Genetics Center in the United States and through the Center's integrated database.

Germany

The Wisconsin RPRC provides training in performance of assays and support for research and development for assays, to the University of Hannover, for studies of captive and free-living dwarf mouse lemurs from Madagascar. These studies are redefining the previous understanding of pheromonal, social, and seasonal regulation of male reproduction in this prosimian species. Novel fecal assays are being developed in collaboration with the Wisconsin RPRC.

Indonesia

The Washington RPRC, Seattle, continues to support collaborative research, training, and a program for breeding nonhuman primates at Bogor Agricultural University. This program has successfully established and maintained a breeding colony of *Macaca fascicularis* that is free of specific pathogens. In the forests of the 600-hectare Tinjil Island, 2,000 *M. fascicularis* now range freely and provide progeny for AIDS-related research at the Washington RPRC and other research facilities supported by the National Institutes of Health. Additionally, the program has established and maintained a breeding colony of *Macaca nemestrina* at Bogor Agricultural University, which provides primates free of simian retrovirus for use in AIDS-related research. The Virology Laboratory, an integral component of the collaboration at the university, conducts all simian retrovirus screening procedures necessary for the colony.

Personnel at the Washington RPRC have conducted educational field-training courses that accommodate both U.S. and Indonesian students. This program continues to serve as an excellent model of international collaboration in the development of primate resources and also serves as a prototype of natural habitat breeding facilities for future primate resources from the country of origin.

Italy

With support from NCRR's Biomedical Technology area, Gruppo Biomed Mod, Padua, is developing new software to solve the problems of estimating input for biological–physiological systems by deconvolution. (In deconvolution, the system response and the input signal are used to produce an estimate of the system model.) To achieve this goal, researchers will develop the theory, numerical algorithms, and software tools through which input signals of these systems and the time course of the signals can be estimated from measured outputs. (Actual measurement of input signals is not possible.) Key to the success of this research effort is development of new numerical algorithms, without which new theories are useless. The combination of theory and novel algorithms will drive the development of software tools, permitting physiological and clinical investigators to solve real-world deconvolution problems.

Mexico

NCRR supports the subcontract of Pangea Systems, Inc., Oakland, California, with Universidad Nacional Autonoma de Mexico, Mexico City, to maintain and expand the publicly accessible EcoCyc database on the World Wide Web. This database describes all known genes and metabolic pathways of *Escherichia coli* and other microbes.

Russia

The Washington RPRC continues to maintain a collaborative program with the Institute of Medical Primatology near Sochi, in southern Russia. This program has provided Russian-bred *M. nemestrina* for research and new sources of *Papio anubis cynocephalus* for the research needs of the Washington RPRC. The first shipment of *P. anubis* was received in October 1998 and will be used in collaborative research programs with departments in the University of Washington School of Medicine, Seattle.

United Kingdom

The NCRR-supported Wisconsin RPRC provides serum samples from prenatally androgenized female rhesus monkeys to the Medical Research Council Reproductive Biology Unit, University of Edinburgh, Scotland. The scientists are investigating common problems in women's health. These samples will enable development of assays for inhibins as serum biomarkers for impaired development of ovarian follicles. Other researchers from the Wisconsin RPRC and the Mayo Clinic, Rochester, Minnesota, are using the prenatally androgenized female rhesus monkeys as models for polycystic ovarian syndrome and for ovarian hyperstimulation.

International Meetings

Organization for Economic Cooperation and Development

The NCRR Director serves as the U.S. representative to the Organization for Economic Cooperation and Development Working Party on Biotechnology Steering Group on Scientific and Technological Infrastructure. In July 1998, this group met in Paris, France, to discuss and plan a workshop that will focus on biological resource centers for microbes, animal cells, and plant cells. The workshop, to be held in Tokyo, Japan, in February 1999, will include discussions to define the benefits and rationale for these centers, benefits and rationale for international coordination, and principles for funding.

Nonhuman Primate Models for AIDS Research

The NCRR-supported Yerkes RPRC organized and hosted the 16th Annual Symposium on Nonhuman Primate Models for AIDS Research, in Atlanta, Georgia, in October 1998. Approximately 300 scientists performing AIDS-related research attended and participated in the meeting. These scientists represented Congo, England, Gabon, Germany, Japan, the Netherlands, Sweden, the United States, and other countries. This annual meeting has become one of the premier workshops on AIDS research in primates. Reports were presented in research areas of AIDS-associated infections, primate immunology, pathogenesis, and vaccines and therapeutic agents.

Harmonization of Nomenclature and Methods in Laboratory Animal Research

In October 1998, NCRR participated in the Workshop on Harmonization of Nomenclature and Methods in Laboratory Animal Research, in Washington, D.C. The purpose of this workshop was to discuss the need for microbiologically and genetically defined mice and rats, definitions that would facilitate the sharing of information between the United States and Japan. The workshop was sponsored by the Institute for Laboratory Animal Research of the National Academy of Sciences.

XXIV.
Center for Information Technology

INTRODUCTION

Created in March 1998, the Center for Information Technology (CIT) combines the functions of the former Division of Computer Research and Technology, the Office of Information Resources Management, and the Telecommunications Branch of the National Institutes of Health (NIH). CIT's mission is to provide, coordinate, and manage information technology and to advance computational science. As part of this mission, CIT performs the following functions:

- acts as a leader in developing policy and standards within the NIH by identifying and communicating issues related to NIH information technology, as well as problems and solutions;
- establishes and operates the necessary organization and infrastructure to ensure computer security, connectivity, and interoperability across the NIH;
- provides leadership for determining NIH's computational and telecommunications needs and oversees development of infrastructure support;
- operates a state-of-the-art regional computer facility responsive to the NIH mission;
- formulates NIH policy on information technology and assists with development of related legislation;
- serves as a Federal Data Center for administrative, biomedical, and statistical computing; and
- provides data processing and high-performance computing facilities, integrated telecommunications data networks, and other information technology services to the U.S. Department of Health and Human Services and various Federal agencies.

In other organizational changes, CIT's Laboratory of Structural Biology moved to the National Institute of Child Health and Human Development in October 1997, and the Molecular Graphics and Simulation Section of the Laboratory moved to the National Heart, Lung, and Blood Institute in November 1997.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

In fiscal year 1998 (FY 98), CIT scientists collaborated extensively with scientists from Canada, China, France, India, Israel, Italy, Japan, New Zealand, Russia, Slovenia, Switzerland, and the United Kingdom. Scientists from many African, Asian, Caribbean, and Latin American countries visited CIT and exchanged information with CIT scientists and technical staff.

The Computational Bioscience and Engineering Laboratory (CBEL) collaborated with a Visiting Scientist from Israel in investigating new techniques related to Doppler ultrasound imaging of cardiac function. This effort, entitled Method and System for Doppler Ultrasound Measurement of Blood Flow, resulted in the award of a U.S. patent to the NIH on December 30, 1997. The patent describes a method for providing Doppler data corrected for misalignment between the direction of flow within a vessel and the beam orientation of an ultrasound probe. In addition, the patent describes a new system for measuring and recording experiment time and free space position and orientation of an ultrasound probe. This method has been added to a conventional ultrasonic Doppler color flow mapping system. From the identified flow direction and the information on orientation and position for each acquired two-dimensional ultrasound image slice, the two-dimensional Doppler signals are appropriately transformed into corrected velocity values. These values can then be used to construct a three-dimensional flow field as a function of time. This method may be shown to extend the diagnostic quality and range of this technology.

In early 1998, representatives of the Radiation Effects Research Foundation, a joint Japanese-U.S. research organization studying radiation-related health effects of the Hiroshima and Nagasaki atomic bombings, toured several prominent U.S. research centers, including the NIH. Two staff members of the foundation's Department of Information Technology visited CIT, where they were given an overview of CIT's Office of Computational Bioscience and demonstrations of services provided by the Scientific Computing Resource Center, the Center for Molecular Modeling, and the Radiology Consultation WorkStation (RCWS) project at the National Cancer Institute's Radiation Oncology Branch in the Warren Grant Magnuson Clinical Center (Clinical Center).

In April 1998, the U.S. Information Agency's *Voice of America* sponsored a 3-day seminar on Broadcasting Health, which was related to electronic media programs dealing with children's health. In their visit to the NIH, 30 participants from radio stations in Africa, Asia, the Caribbean, and Latin America received a CIT presentation on Telemedicine—Medical Advice and Patient Treatment via Live Video, including a demonstration of RCWS, which was developed by staff of CBEL. CIT demonstrated the potential that the high-speed RCWS environment can provide for effective communication between geographically distant locations. Using the RCWS system, which is based on asynchronous transfer mode networking technology, a simulated medical teleconference was conducted between two buildings on the NIH campus, Bethesda, Maryland.

During FY 98, a Special Volunteer who is a senior scientist from the Karpov Institute of Physical Chemistry, Moscow, Russia, worked in CIT's Mathematical and Statistical Computing Laboratory (MSCL). He developed theoretical and computer-oriented techniques for calculating conformational and environmental effects on the dynamic behavior of chemical reactions in biologically important systems. In September 1998, another scientist from the Karpov Institute of Physical Chemistry joined MSCL researchers to extend the research on this project. The Special Volunteer also assisted MSCL researchers in preparing a monograph on the theory of rate processes as applied to certain identified chemical reactions. In addition, he has made many important contributions in the application of Kramer's model for calculating reaction rates.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

In March 1998, a CIT-sponsored seminar, entitled Reversible Peptide Folding in Solution by Molecular Dynamics Simulation, was presented by a scientist from the Swiss Federal Institute of Technology, Zürich.

In July 1998, an associate professor from the Electrical, Electronics, and Computer Science Department, University of Trieste, Italy, visited CBEL to view the RCWS Project with a colleague from the National Eye Institute.

In September 1998, a visiting scientist from the Karpov Institute of Physical Chemistry, Moscow, Russia. gave a seminar on Modern Continuum Theories of Solvation and Their Application to Electron Transfer Reactions.

International Meetings

CIT participated in the following international meetings in FY 98:

- 19th Annual International Conference of the IEEE (Institute of Electrical and Electronics Engineers, Inc.) Engineering in Medicine and Biology Society, in Chicago, Illinois, in October 1997;
- Supercomputing '97: High Performance Computing and Communications Conference, in San Jose, California, in November 1997;
- International Society for Optical Engineering Medical Imaging Conference, in San Diego, California, in February 1998;
- 12th International Parallel Processing Symposium and 9th Symposium on Parallel and Distributed Processing, in Orlando, Florida, in March 1998;
- IEEE International Conference on Information Technology Applications in Biomedicine, in Washington, D.C., in May 1998;
- Federation of American Societies for Experimental Biology Summer Research Conferences: Virus Assembly, in Saxton's River, Vermont, in July 1998;
- 23rd International Herpesvirus Workshop, in York, England, in August 1998;
- 14th International Congress on Electron Microscopy, in Cancún, Mexico, in August 1998;
- 24th International Conference on Very Large Data Bases, in New York, New York, in August 1998; and
- Bioinformatics for the Future, in Basel, Switzerland, in September 1998.

Intramural Programs and Activities

Visiting Scientists and Visiting Associates from Canada, China, France, Germany, India, New Zealand, Russia, Slovenia, and the United Kingdom worked with CIT investigators on various collaborative research projects.

While serving as a Special Volunteer in MSCL's Analytical Biostatistics Section, an Honorary Director of Research from France's National Institute of Agronomic Research collaborated on several projects:

1. extension of a library of hidden Markov models to include all known protein-folding topologies;
2. application of Markov models to orphan sequences from genomic databases to identify possible sequence function; and
3. enhancement of the NIH server used for predicting protein structure, to provide new versions of several constituent programs, allowing access to the best available prediction algorithms.

A Visiting Associate in MSCL, who works on several instrumental analysis projects, collaborated with researchers at the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke on problems of representation and statistical analysis of diffusion tensor imaging data. This Visiting Associate, who is a member of the Clinical Center's Diagnostic Radiology Department, is also working with MSCL researchers to develop a wavelet-based method for compression of images. Because initial studies using computed tomography scans produced promising results, the researchers expect to apply the method to larger digital, chest x-ray images.

In the Cancer Genome Anatomy Project, the Visiting Associate is working with MSCL staff to develop microarray technology using cDNA (complementary DNA) for analysis of patterns of gene expression. An algorithm for rapid deconvolution has been used to correct for the spillover of neighboring peak activity due to the proximity of imaged peaks in the microarray.

CBEL's High Performance Biomedical Computing Section collaborated with a Fogarty Fellow from China and a Visiting Scientist from Germany on maximum likelihood reconstruction of images from positron emission tomography.

Researchers in this Section also collaborated with a Visiting Scientist from India on the reconstruction and registration of electron paramagnetic resonance images.

CBEL's Biomedical Image Processing Section collaborated with Visiting Scientists and Visiting Associates from Canada, China, Japan, New Zealand, and the United Kingdom on determination of macromolecular structure by using images from electron microscopy. Of particular interest is the structure of selected viruses (herpes simplex virus, cytomegalovirus, papillomavirus, bacteriophage T4, and HIV-1 Rev protein) and bacterial components and other macromolecular structures. Joint research projects included the following:

- electron microscopy on viruses, proteins, and macromolecules;
- methods for improving resolution of three-dimensional reconstruction from cryoelectron micrographs;
- study of the structure of helical filaments of the HIV-1 Rev protein filaments;
- determination of the three-dimensional structure of papillomavirus; and
- elucidation of the three-dimensional structure of bacteriophage T4.

A Russian Visiting Scientist, who joined the Center for Molecular Modeling in August 1998, is investigating molecular modeling and prediction of protein structures.

XXV.
Center for Scientific Review

INTRODUCTION

The Center for Scientific Review (CSR), formerly the Division of Research Grants, is the central receipt point for approximately 40,000 grant applications submitted to the Public Health Service per year. The Center provides the review for scientific and technical merit for most of the applications submitted to the National Institutes of Health (NIH) through more than 120 study sections clustered by scientific areas into approximately 20 initial review groups. Review meetings of research scientists from outside the NIH are convened by scientific review administrators of CSR to provide expertise in biomedical and behavioral research. These experts conduct rigorous and equitable review of the merit of applications for support for research and research training. In addition, CSR continues to cooperate actively with organizations in other countries that have an interest in identifying and supporting high-quality biomedical and behavioral research.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

CSR was represented in a delegation of NIH representatives and representatives from the U.S. Department of Energy, the National Science Foundation, the U.S. Department of Agriculture, the U.S. Department of State, and the U.S. Geological Survey. The delegation participated in workshops in Prague, Budapest, and Piestany to discuss U.S. international grant programs with scientists and officials of the Czech Republic, Hungary, and Slovakia, respectively. One intent was to provide information on grant support to scientists in these countries. The workshops provided the opportunity to discuss the grant process with foreign scientists and to make suggestions for preparation of more competitive grant proposals.

The Director currently in charge of the review and evaluation of research at the Chinese National Academy of Sciences spent 6 months at the NIH on a visit that was hosted and organized by CSR staff. She visited NIH extramural programs in many of the Institutes and at George Washington University, Washington, D.C., and attended study section meetings to observe reviews of grant applications.

In fiscal year 1998, CSR hosted two delegations of scientists from China representing engineering and physical and health sciences and many international visitors who came to study the referral and peer review procedures and recent innovations that have been introduced to improve, expedite, and streamline the processes. These visitors were from Armenia, England, Germany, Japan, Russia, Saudi Arabia, Sweden, and Taiwan.

XXVI.
Warren Grant Magnuson Clinical Center

INTRODUCTION

As the research hospital for the National Institutes of Health (NIH), the Warren Grant Magnuson Clinical Center supports clinical investigations conducted by the Institutes. The Clinical Center was specifically designed to bring patient care facilities close to experimental laboratories to facilitate and expedite the testing and application of basic research findings in the treatment of patients. The 14-story, 325-bed facility employs 500 nurses, 570 allied health professionals, and 1,200 credentialed physicians, dentists, and doctorate-level researchers.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

The Clinical Center participated in a variety of international activities during fiscal year 1998 (FY 98). Staff presented research findings at numerous international conferences on subjects such as stem cell transplantation and cytokines; brain tumors and spinal imaging; use of magnetic resonance imaging (MRI) in multiple sclerosis; risk factors from low doses of ionizing radiation; disability in arthritic conditions; and intervention through occupational therapy in dementia.

Staff was also involved with the formulation and distribution of investigational medications and collaboration with international researchers in diverse fields of clinical investigation.

DEPARTMENT OF ANESTHESIA AND SURGICAL SERVICES

The Department of Anesthesia and Surgical Services hosted several foreign visitors interested in the unique surgical protocols performed at the Clinical Center. In FY 98, an Israeli orthopedic surgeon consulted with the anesthesia and surgical staff about a procedure he performs in Israel. Surgeons at the Clinical Center may start to use the procedure if it is approved by the Institutional Review Board. Polish and Russian neurosurgeons observed neurosurgical procedures in the surgical suite.

CLINICAL PATHOLOGY DEPARTMENT

Members of the Clinical Pathology Department participated in several international activities during FY 98.

Clinical Chemistry Service
International Research

Investigators in the Clinical Chemistry Service collaborated with researchers from the University of Amsterdam, the Netherlands, in the evaluation of new ion-selective electrode methods for measuring ionized magnesium in serum.

Hematology Service
International Research

A Visiting Fellow from Saga Medical School, Japan, finished research projects in the Hematology Service. These studies assessed levels of plasma glycocalicin as an indicator of platelet integrity in platelet concentrates and of platelet turnover in patients who were positive for human immunodeficiency virus (HIV). Two reports of the research were published in 1998—one in *Thrombosis Research* and one in the *Journal of Laboratory and Clinical Medicine.*

Immunology Service
International Research

The Director of the AIDS (acquired immunodeficiency syndrome) and Clinical Immunology Research Laboratory, Tibilisi, Georgia, visited the Immunology Service and began efforts to identify investigators in Georgia for research training in the Immunology Service.

Microbiology Service
International Research

In FY 98, a Fogarty Fellow from Canada continued her research and training activities in the Microbiology Service, with special emphasis on (1) development of a molecular test for detection of *Borrelia, Helicobacter,* and *Legionella* species in clinical specimens and (2) basic research on the urease gene of *Helicobacter* species. Together with several other members of the Service, she published a report in the *American Journal of Clinical Pathology,* in September 1998, on a commercially available kit for using polymerase chain reaction to detect *Legionella* in sputum and bronchoalveolar lavage specimens from patients. She also was a coauthor of an abstract on an epidemiologic investigation of a pseudoepidemic resulting from contamination of bronchoscopes with rapidly growing mycobacterium.

A physician from the Pan American Health Organization spent several days with members of the Microbiology Service to get an overview of current diagnostic methods for infectious diseases, with special emphasis on the detection of antimicrobial resistance.

International Meetings

The Fogarty Fellow from Canada gave a poster presentation on *Helicobacter* species as emerging pathogens in patients with AIDS, at the meeting of the Canadian Society of Microbiologists, in Guelph, Ontario, on June 14–18, 1998.

CRITICAL CARE MEDICINE DEPARTMENT
International Research

Seven visiting foreign scientists performed research in the areas of pulmonary disease, HIV, and sepsis, in the Critical Care Medicine Department:

- A Visiting Fellow from Beijing Union Medical College, China, is studying genomic control of the regulation of arachidonate metabolism in epithelial cells.
- A Visiting Fellow from the Chinese Academy of Medical Sciences, Beijing, is

studying interactions between endotoxin and white blood cells.

- A Visiting Fellow from Chongqing University, China, is evaluating mutations in genes of *Pneumocystis carinii* that are the targets of drug therapy, to determine whether resistance to the therapeutic agents is developing.
- A Visiting Fellow from Dalian Medical University, China, is studying responses of lung epithelial cells to inflammation.
- A Visiting Fellow from Hunan Medical University, Changsha, China, is working to develop a rapid diagnostic test for *Pneumocystis*.
- A Visiting Fellow from Tongji Medical University, Wuhan, China, is studying lung inflammatory processes.
- An investigator, formerly at the Hospital General Universitario Gregorio Marnon, Madrid, Spain, is working on mechanisms of cell migration in acute lung inflammation.

DIAGNOSTIC RADIOLOGY DEPARTMENT

Members of the Diagnostic Radiology Department participated in several international activities in FY 98.

International Research

A Special Volunteer from Tokyo, Japan, participated in efforts to improve functional studies by using MRI and stereotactic localization of brain tumors. He became active in the Department's research activities.

International Meetings

Personnel from the Diagnostic Radiology Department participated in various capacities at international meetings during FY 98:

- invited speaker with presentation on petrosal sinus catheterization in Cushing's disease and radiological changes in the spectrum of Cushing's disease, at the IXth International Symposium of Neuroendocrinology, in Rio de Janeiro, Brazil, on October 30–November 1, 1997;
- invited speaker with presentation on urologic MRI, at the meeting of the International Society of Magnetic Resonance in Medicine, in Sydney, Australia, on April 15–22, 1998;
- invited speaker at the Symposium on Immunotherapy of Brain Tumors, in Hamilton, Bermuda, on May 15–18, 1998;
- invited speaker with presentation on cystic masses of the kidney, at the meeting of the Society of Uroradiology, in Hamilton, Bermuda, on July 1–5, 1998;
- invited speaker with presentation on acquired cystic kidney disease, at the meeting of the European Society of Uroradiology, in Strasbourg, France, on September 10–14, 1998;
- invited speaker with presentation on pancreatic neuroendocrine tumors, at the International Symposium on von Hippel-Lindau Disease, in Paris, France, on September 14–18, 1998;
- presenter of the NIH experience with breast MRI, at the meeting of the International Society of Breast MRI, in Dublin, Ireland, on September 14–19, 1998;
- invited speaker with presentations on brain tumors and spinal imaging, at the 11th Annual Pan Hellenic Congress of Radiology, in Salonica, Greece, on September 18–22, 1998; and
- invited speaker with presentation on endocrine radiology, at the meeting of the International Society of Endocrinology, in Dublin, Ireland, on September 30–October 10, 1998.

LABORATORY OF DIAGNOSTIC RADIOLOGY RESEARCH

International Meetings

The Chief of the Laboratory of Diagnostic Radiology Research was invited to present research at the International Symposium on Immunopathology of Multiple Sclerosis, in Vienna, Austria, on November 13–17, 1997. The Laboratory Chief was also invited to present research at the International Workshop on the Use of Magnetic Resonance in Multiple Sclerosis, in Cambridge, England, on November 21–23, 1997.

Staff of the Laboratory of Diagnostic Radiology Research participated in various capacities at several international meetings in FY 98:

- invited speakers and poster presenters at the International Society of Magnetic Resonance in Medicine, 6th Scientific Meeting, in Sydney, Australia, on April 20–24, 1998;
- invited speaker on MRI Measurement of Cerebral Perfusion With Spin Tagging, at the workshop entitled Imaging of Normal and Abnormal Brain Function, at Helsinki University of Technology, Finland, on May 14–17, 1998;
- invited participant at the European Neurological Society Meeting, in Nice, France, on June 6–12, 1998; and
- invited presenter at the 4th International Conference on Functional Mapping of the Human Brain, in Montreal, Quebec, on June 7–12, 1998.

HOSPITAL EPIDEMIOLOGY AND QUALITY ASSURANCE SERVICE

International Research

Investigators in the Hospital Epidemiology and Quality Assurance Service are collaborating with physicians and nurses in university hospitals in Japan on a study designed to accomplish the following purposes:

- to evaluate and compare nurses' knowledge of epidemiology, pathogenesis, occupational risks, and appropriate prevention strategies in relation to infection with bloodborne pathogens;
- to compare self-reported levels of compliance with recommendations for infection control;
- to compare self-reported frequencies of cutaneous exposures to blood; and
- to evaluate the effect of educational interventions on nurses' perceived compliance with recommendations and on the frequencies of self-reported exposures to blood.

International Activities

At the request of the Chinese government, a nurse epidemiologist, in collaboration with a physician from the National Institute of Allergy and Infectious Diseases, traveled to China to provide consultation on the epidemiology and treatment of patients involved in a nosocomial outbreak of nontuberculous mycobacterial infections in a hospital in Shen Zhen Province, China.

International Meetings

During FY 98, the hospital epidemiologist (Deputy Director for Clinical Care, Clinical Center) was an invited speaker with a presentation on Managing Occupational Exposure to Bloodborne Pathogens, at the Quadrennial Meeting of the Hospital Infections Society, in Edinburgh, Scotland, on September 13–15, 1998.

NUCLEAR MEDICINE DEPARTMENT

The Nuclear Medicine Department welcomed the Clinical Center's first Clinical

Fogarty Scholar, who was previously the Director of the Institute of Medicine, Jülich, and Chairman of the Nuclear Medicine Department, University Hospital, Düsseldorf, Germany. He interacts with the Nuclear Medicine Department groups examining the Auger effect on DNA damage and DNA repair and the nuclear cardiology research group using positron emission tomography (PET). His first task was to represent the Nuclear Medicine and Positron Emission Tomography Departments of the Clinical Center, at the 1st Spanish PET Symposium, in Madrid, Spain, on June 22–23, 1998. He organized a symposium on Modern Aspects of Radionuclide Therapy and Radiation Risks, for the combined meetings of the European Association of Nuclear Medicine and the World Federation of Nuclear Medicine and Biology, in Berlin, Germany, on August 30–September 3, 1998.

International Research

Two Visiting Fellows from France worked with the Imaging Science Group of the Nuclear Medicine Department. They collaborated on research to quantify uptake of tracers by using PET and on developing better methods to reconstruct images from both positron emission and single photon tomography. The results of these investigations were applied to imaging for both cardiac disease and cancer.

Three Fogarty Fellows, one from Japan and two from Korea, worked on development of radiolabeled Fv fragments as diagnostic imaging agents for cancer. This work resulted in presentations at the national meeting of the Society of Nuclear Medicine and a presentation at the 7th Conference on Radioimmunodetection and Radioimmunotherapy of Cancer, in Princeton, New Jersey, in October 1998.

International Meetings

Personnel of the Nuclear Medicine Department participated in several international meetings in FY 98:

■ A staff physician attended the scientific sessions of the XIIIth World Congress of Cardiology, in Rio de Janeiro, Brazil, in April 1998.

■ A senior member of the Imaging Physics Laboratory organized and conducted a symposium entitled Animal Imaging in Nuclear Medicine: Advanced Instruments, Methods, and Applications, which was presented by Canadian, U.S., and foreign scientists for an international audience at the annual meeting of the Society of Nuclear Medicine, in Toronto, Ontario, in June 1998.

■ A Visiting Fellow from Spain, in the Imaging Physics Laboratory, was invited to make a presentation on Technical Aspects of PET Imaging, at an international symposium on PET in Diagnosis and Follow-up of Oncological Patients, in Madrid, Spain, in July 1998.

■ The same Visiting Fellow from Spain was also invited to conduct a short course entitled How and With What Are Medical Images Created? The course was sponsored by the Universidad Nacional de Educación a Distancia, in Pontevedra, Spain, in July 1998.

■ The Chief of the Department gave an invited presentation entitled The Auger Effect in Preclinical and Clinical Trials for Cancer Therapy, at the 7th World Congress of Nuclear Medicine and Biology, in Berlin, Germany, in August 1998.

■ The Clinical Fogarty Scholar gave an invited presentation on Risk Factors From Low Doses of Ionizing Radiation, at the 7th World Congress of Nuclear Medicine and Biology, in Berlin, in August 1998, and lectured on Low-Dose Effects, at the National Laboratory of Radiation Research, Chiba, Japan, on August 21, 1998. This scientist also participated in the Annual Meeting of the International Commission on Radiation Units and Measurements, as a member of the commission. The meeting was held in Chiba, on August 23–28, 1998.

■ The Clinical Fogarty Scholar also presented a report entitled Low-Dose Irradiation Appears to Reduce Endogenous DNA Damage, at an international symposium in Bad-Hofgastein, Austria, on September 28–30, 1998.

■ A senior member of the Imaging Sciences Group was invited to present a seminar on methods for quantifying tracer uptake in PET, in Paris, France. This staff physicist was also invited by Institut National de la Santé et de la Recherche Médicale (INSERM) to present a seminar on the same topic, at Hôpital Pitié-Salpêtriére, Paris. In addition, he was invited to serve as a committee member for the habilitation examination of a former NIH fellow.

NURSING DEPARTMENT

Members of the Nursing Department continued to be active internationally in FY 98.

International Meetings

Nursing Department staff participated in various capacities at international meetings during FY 98:

■ presented oncology updates to Chilean nurses and physicians, in Santiago, Chile, in December 1997, in a collaborative effort between the Chilean Oncology Society and the National Cancer Institute of Chile, which was funded by Chile;

■ cochaired a symposium and presented a research report entitled Timing and Costs of Nursing Interventions in the Intensive Care Unit, at the 3rd International Conference on Advances in Pulmonary Rehabilitation and Management of Chronic Respiratory Failure, in Florence, Italy, on March 11–14, 1998;

■ gave a presentation on Relationships Among Personality Traits, Coping Styles, and Quality of Life in Patients with Alpha-1 Antitrypsin Deficiency, at the International Conference of the American Thoracic Society, in Chicago, Illinois, on April 24–29, 1998;

■ received an Oncology Nursing Society scholarship to attend the 17th International Cancer Congress of the International Union Against Cancer (UICC), in Rio de Janeiro, Brazil, in August 1998 (Quality of Life and Breast Cancer Survivors presented in medical symposium and published in *Cancer Practice;* Risk Factors for the Gynecologic Cancers presented in nursing symposium); and

■ invited to return to Chile and presented additional oncology nursing curriculum, in Spanish, to nursing colleagues in Chile, in September 1998.

Intramural Programs and Activities

In FY 98, the Nursing Department hosted 63 international visitors and provided international nursing faculty and students with learning opportunities in clinical care, research, education, and informatics. These activities provide an opportunity for sharing expertise and experience across a wide spectrum of issues. The Nursing Department is frequently consulted through contacts at international conferences and courses or through the Internet, about the Department standards of practice for nursing and for care of patients.

The Nursing Department provided a host site for the International Oncology Nursing Fellowships. Nurses from Eastern European countries received training related to cancer prevention and early detection, teaching of patients, safe administration of cytotoxic agents, pain management, quality-of-life issues, and research. A nurse from Malta who completed the training implemented a comprehensive oncology educational course in her home institution.

In addition, the Nursing Department sponsored the Psychiatric Nursing Faculty Internship Program, with attendees from Canada, South Africa, and the United States; served as host to a graduate student in psychiatric nursing from Thailand, through the Catholic University of America, Washington, D.C., in the spring of 1998; and hosted a visitor from Taiwan, to provide an overview of the National Cancer Institute and the NIH, in May 1998.

In August 1998, the Department provided an intensive nursing informatics internship, to assist international faculty from Khon Kaen University, Thailand, in understanding applications of nursing informatics in a clinical practice setting. The student will use the information to establish an informatics program for nurses in Thailand.

PHARMACY DEPARTMENT

Members of the Pharmacy Department participated in several international activities during FY 98.

International Research

Formulation and distribution of investigational medications to Argentina, Chile, China, Thailand, the United Kingdom, and Vietnam were part of ongoing studies with NIH-based investigators.

International Meetings

One staff member was an invited speaker at the 6th International Symposium on Oncology Pharmacy Practice, in Mexico City, Mexico, on March 26–29, 1998.

In addition, personnel from the Pharmacy Department reported research activities at the international 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, in San Diego, California, on September 24–27, 1998.

NIH Campus Activities

Activities of the Pharmacy Department on the NIH campus in Bethesda, Maryland, included the following:

- Guests from China, Japan, Russia, and Slovenia visited for 1-day programs to learn about pharmacy practice or pharmaceutical science.
- A guest pharmacy researcher from Italy spent several weeks in the Pharmacy Department learning modern concepts related to searching for information on drugs.
- Educational programs on use of medications and compliance were provided for the Infectious Disease Society of America Training Program in AIDS, to registrants from Armenia, El Salvador, and Poland.
- Pharmacy Department staff chaired the Pharmacokinetics-Pharmacodynamics Practice and Research Network in the American College of Clinical Pharmacy (worldwide network of pharmacokineticists).

POSITRON EMISSION TOMOGRAPHY DEPARTMENT

Members of the Positron Emission Tomography Department participated in several international research activities in FY 98:

- collaboration with a Special Volunteer from Italy to develop ^{11}C- and ^{18}F-radiolabeled diazepam derivatives during a 3-month stay;
- work with a Visiting Fellow from Japan to develop a method to predict defluorination in vivo, on the basis of in vitro tests; and
- joint efforts between the Positron Emission Tomography Department and a major European laboratory, to develop muscarinic receptor ligands.

REHABILITATION MEDICINE DEPARTMENT

International Meetings

Members of the Rehabilitation Medicine Department participated in various capacities in international meetings in FY 98:

- The Chief, Rehabilitation Medicine Department, was an invited speaker at the meeting of the Asian Pacific League Against Rheumatism, in Manila, Philippines, on January 16–22, 1998, and copresented a symposium on Foot Evaluation and Management, for the Physical Medicine and Rehabilitation Department, University of Santo Tomás, Manila.
- The Chief also participated in a symposium entitled Exercise for the Elderly, sponsored by the Department of Physical Medicine and Rehabilitation, University of Puerto Rico, San Juan, on March 12–13, 1998.
- The research coordinator of the Rehabilitation Medicine Department gave a presentation on Occupational Therapy Intervention in Dementia, at the 4th International Assessment of Motor and Process Skills Symposium, in Umeå, Sweden, on October 8–10, 1998.
- The research coordinator also hosted a contingent of occupational therapists from the Karolinska Institute, Stockholm, Sweden. Future collaborative efforts with the Karolinska Institute are being explored and may include the Swedish translation of an outcome measure developed in the Rehabilitation Medicine Department.

Biomechanics Section

International Research

The Chief, Biomechanics Section, continued to support a collaborative research effort of the National Institute of Neurological Disorders and Stroke, NIH, with the National Research Institute on Aging, Florence, Italy.

The Chief has been elected vice president of the board of directors of the Commission for Motion Laboratory Accreditation. The Chief is also a member of an international team of scientists and clinicians that has the task of developing guidelines for future editions of software for analysis of human movement. The Biomechanics Section software for motion analysis continues to be licensed through agreements for transfer of materials to scientists in Australia, Canada, England, Ireland, Italy, and the Netherlands.

International Meetings

Staff of the Biomechanics Section attended the annual international meeting of the Gait and Clinical Movement Analysis Society, in San Diego, California, on April 15–18, 1998.

Speech-Language Pathology Section

International Research

The research speech-language pathologist of the Speech-Language Pathology Section delivered a keynote address and conducted a half-day workshop on outcomes research, entitled Expanding Horizons, at the National Conference of the Speech-Language

Pathology Association of Australia, Fremantle, Western Australia, on May 11–15, 1998. Presentations focused on outcomes research, technology, and computer applications to clinical management, as well as applications of clinical research to clinical practice.

International Meetings

The Chief, Speech-Language Pathology Section, was invited to Tel Aviv, Israel, to teach the first university graduate course on Dysphagia: Swallowing and Its Disorders, for speech-language pathologists in Israel. This newly developed course was taught at Tel Aviv University, Department of Communication Disorders, in the Medical School's Sackler School of Health Professions. The Chief, Speech-Language Pathology Section, also met with the faculty of the Departments of Dentistry and Otolaryngology and presented a research seminar for the medical residents and medical staff on Swallowing Outcomes in Head and Neck Cancer. In addition, the Chief conducted a special symposium on Assessment of Dysphagia, for the Israel Speech and Hearing Association, Tel Aviv.

The Section Chief presented a colloquium on Three-Dimensional Ultrasound Imaging, for the faculty and graduate students of the Biomedical Engineering Department, Technion Institute, Haifa, Israel.

The Chief served on the program planning committee for the Dysphagia Research Society's annual meeting. This group of multidisciplinary international scientists conducts investigations on swallowing and its disorders, in many world centers.

DEPARTMENT OF TRANSFUSION MEDICINE

In FY 98, eight Visiting Fellows (five from China, one from Germany, and two from Japan) worked with staff of the Department of Transfusion Medicine. Two Special Volunteers, one from Norway and the other from the Blood Transfusion and Hematology Center in Vietnam, also worked with Department staff.

International Meetings

Several staff members participated in international meetings.

The Chief of the Department of Transfusion Medicine served in the following capacities:

- invited speaker with presentation on Future Trends in Transfusion Techniques, at the conference on Building a Better Blood System for the 21st Century, in Toronto, on November 2–4, 1997;
- invited participant at the 1998 Hemiquinquennial Strategic Planning Meeting of the U.S. Pharmacopeia, in San José, Costa Rica, on March 7–14, 1998;
- invited scientific reviewer at the Research Review Committee for the British Blood Authority, in London, England, on March 28–April 1, 1998; and
- invited speaker with presentation on Stem Cell Transplantation and Cytokines, at the 31st Congress of Deutsche Gesellschaft für Transfusionmedizin und Immunohematologie, in Zürich, Switzerland, on October 6–10, 1998.

The Chief of the Infectious Diseases Section acted in the following capacities:

- invited speaker on the Natural History of Hepatitis A and G, at the Pan Caribbean Conference on Hemophilia, in San José, Puerto Rico, on March 4–7, 1998;
- invited speaker with presentation on The History of Hepatitis C and Hepatitis G, at the Argentina Association for the Study of Liver Disease and Natural History of Hepatitis C, in Buenos Aires, on April 21–26, 1998;
- invited speaker with presentation entitled Hepatitis A to G, at the XXIIIrd International Congress of the World Federation of Hemophilia, in The Hague, the Netherlands, on May 16–23, 1998;
- invited speaker on Natural History of Hepatitis C, at the international meeting on Hepatitis C Virus, in Venice, Italy, on June 25–28, 1998;
- elected councilor (senior advisor) at the meeting of the International Society of Blood Transfusion, in Oslo, Norway, on June 28–July 4, 1998; and
- chairman of the 23rd International Symposium on Blood Transfusion, entitled Risk Management in Blood Transfusion: the Virtue of Reality, in Groningen, the Netherlands, on October 6–10, 1998.

A staff member of the Infectious Diseases Section was an invited speaker with presentations on (1) The Role of Molecular Biology in Blood Cell Testing and (2) Granulocyte Transfusions, at the meeting of the International Society of Blood Transfusion, in Beijing, China, on October 29–November 7, 1997. This staff member was also an invited speaker with presentations on (1) Implementing Quality in Blood Banks: the U.S. Experience and (2) Molecular Diagnostics in Hepatitis C Infection, at the 23rd World Congress of Medical Technology, in Singapore, on June 27–July 4, 1998.

Three members of the HLA (human leukocyte antigen) Laboratory attended the meeting of the American Society of Histocompatibility and Immunogenetics, in Vancouver, British Columbia, on October 9–14, 1998. One researcher made a poster presentation and gave a report on Molecular Screen for HLA Genotypes.

Appendix A
Abbreviations and Acronyms

A

ACTH	adrenocorticotropic hormone
AIDS	acquired immunodeficiency syndrome
AIDS-FIRCA	HIV/AIDS and Related Illnesses FIRCA
AITRP	AIDS International Training and Research Program
ALSPAC	Avon Longitudinal Study of Pregnancy and Childhood
AMAP	Arctic Monitoring and Assessment Program
anti-HCV	antibody to hepatitis C virus
anti-HTLV	antibody to human T-cell leukemia/lymphoma virus
ARIC	Atherosclerosis Risk in Communities
AT	ataxia-telangiectasia
AZT	zidovudine

B

BAMS	Basic Applied Myology Society
BAP	Biology of Aging Program
BARI	Bypass Angioplasty Revascularization Investigation
BCG	bacille Calmette-Guérin
BITNIS	Batch Internet-NLM Intercommunication Service
BLSA	Baltimore Longitudinal Study of Aging
BMRI	Baker Medical Research Institute
BSE	bovine spongiform encephalopathy
BSP	bone sialoprotein

C

CABG	coronary artery bypass graft
CAPS	Center for AIDS Prevention Studies
CBEL	Computational Bioscience and Engineering Laboratory
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
cDNA	complementary DNA
CF	cystic fibrosis
CIDI	Composite International Diagnostic Interview
CIT	Center for Information Technology
CJD	Creutzfeldt-Jakob disease
CMSP	Cooperative Medical Sciences Program
COCs	combined estrogen–progestogen oral contraceptives
COPD	chronic obstructive pulmonary disease
CRADA	Cooperative Research and Development Agreement
CRC	Cancer Research Campaign
CRDF	U.S. Civilian Research and Defense Foundation
CSR	Center for Scientific Review
CTEP	Cancer Therapy Evaluation Program
CVD	cardiovascular disease
CVRI	Cardiovascular Research Institute

D

DAIDS	Division of AIDS
DDT	dichlorodiphenyltrichloroethane
DECA	Division of Epidemiology and Clinical Applications
Deet	*N,N*-diethyl-*m*-toluamide
DESPR	Division of Epidemiology, Statistics, and Research
DHHS	U.S. Department of Health and Human Services
DIR	Division of Intramural Research
DMID	Division of Microbiology and Infectious Diseases
DMPA	depot medroxyprogesterone acetate
DMPS	2,3-dimercapto-1-propanesulfonic acid
DPE	Demography and Population Epidemiology
DTP	Developmental Therapeutics Program

E

EBV	Epstein-Barr virus
EDB	Epidemiology, Demography, and Biometry
ELISA	enzyme-linked immunosorbent assay
e-mail	electronic mail
EORTC	European Organization for Research and Treatment of Cancer
EPA	U.S. Environmental Protection Agency
ETEC	enterotoxigenic *Escherichia coli*

F

FAK	focal adhesion kinase
FAS	fetal alcohol syndrome
FDA	U.S. Food and Drug Administration
FDI	Fédération Dentaire Internationale
FGF	fibroblast growth factor
FIC	Fogarty International Center
FIOCRUZ	Oswaldo Cruz Foundation
FIRCA	Fogarty International Research Collaboration Award
FMF	familial Mediterranean fever
FY	fiscal year

G

GC-MS	gas chromatography-mass spectroscopy
GCRC	General Clinical Research Center
GINA	Global Initiative for Asthma
GnRH	gonadotropin-releasing hormone

NIDR	National Institute of Dental Research
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NIMHANS	National Institute of Mental Health and Neurosciences
NINDS	National Institute of Neurological Disorders and Stroke
NINOS	Neonatal Inhaled Nitric Oxide Study
NINR	National Institute of Nursing Research
NIS	Newly Independent States of the Former Soviet Union
NLM	National Library of Medicine
NNA	Neuroscience and Neuropsychology of Aging
NO	nitric oxide
NRSA	National Research Service Award
NTP	National Toxicology Program

O

OAR	Office of AIDS Research
ODA	Office of Demography of Aging
ODS	Office of Dietary Supplements
OECD	Organization for Economic Cooperation and Development
OIA	Office of International Affairs
OIH	Office of International Health
OMIM	Online Mendelian Inheritance in Man
OMNI	Online Medical Networked Information
OPRR	Office for Protection From Research Risks
ORD	Office of Rare Diseases
ORMH	Office of Research on Minority Health
ORWH	Office of Research on Women's Health

P

P01	program project
PAHO	Pan American Health Organization
PAHs	polyaromatic hydrocarbons
PAVE	Preparing for AIDS/HIV Vaccine Evaluation
PCBs	polychlorinated biphenyls
PCDFs	polychlorinated dibenzofurans
PCG	primary congenital glaucoma
PCR	polymerase chain reaction
PDAY	Pathobiological Determinants of Atherosclerosis in Youth
PDH	pyruvate dehydrogenase
PDQ	Physician Data Query
PET	positron emission tomography
PHC	primary hepatocellular carcinoma
PHS	U.S. Public Health Service
POMC	proopiomelanocortin
PPD	purified protein derivative
PROVA	Progetto Veneto Anziani
PTCA	percutaneous transluminal coronary angioplasty
PTSD	post-traumatic stress disorder
PVOs	private voluntary organizations

R

RCMM	Research Center for Molecular Microbiology
RCWS	Radiology Consultation WorkStation
R&D	research and development
REVES	Réseau Espérance de Vie en Santé
RFA	Request for Applications
RPRC	Regional Primate Research Center
rRNA	ribosomal RNA
RSANET	Reproductive Sciences of the Americas Network

S

SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SIDS	sudden infant death syndrome
SIV	simian immunodeficiency virus
SNS	sympathetic nervous system
STD	sexually transmitted disease
STLV	simian T-cell leukemia/lymphoma viruses

T

TB	tuberculosis
TDRU	Tropical Disease Research Unit
TGF	transforming growth factor
TH	helper T cell
TMJ	temporomandibular joint
TMRC	Tropical Medicine Research Center
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone

U

UCLA	University of California, Los Angeles
UDP	uridine diphosphate
UICC	International Union Against Cancer
UNAIDS	United Nations AIDS
UNESCO	United Nations Educational, Scientific, and Cultural Organization
USAID	U.S. Agency for International Development
USDA	U.S. Department of Agriculture
U.S.-EC	U.S.-European Commission

V

VWF	von Willebrand factor

W

WHO	World Health Organization

Appendix B
Definitions of NIH International Program Activities

RESEARCH

Foreign Research Grants

The National Institutes of Health (NIH) supports research projects outside the United States only when such projects have met special criteria established for foreign grants. These criteria include high scientific merit relevant to the program interests of the NIH, unique or special resources, and potential for significantly advancing the health sciences in the United States.

Domestic Grants With Foreign Components

A domestic grant with a foreign component is an NIH-financed grant to a domestic institution in which a part of the grant is used to support research in a foreign country.

Cooperative Agreements

Cooperative agreements are assistance awards to foreign or domestic institutions in which substantial programmatic involvement is anticipated between the NIH and the recipient during performance of the contemplated activity.

International Scientific Meetings

The NIH assists in the support of scientific meetings held to coordinate, exchange, and disseminate information when such activities are directed toward objectives clearly within the area of NIH program interests. Activities reported include international components of those meetings supported under this research program area.

Special Foreign Currency (Public Law 480) Grants

The Special Foreign Currency Program, administered by the Fogarty International Center (FIC), enables the NIH to support overseas activities that contribute to the advancement of health sciences in the United States. Funded by U.S.-owned local excess currency derived primarily from the sales of surplus U.S. agricultural commodities, these activities include biomedical research and the translation and dissemination of scientific literature. Funds for the Special Foreign Currency Program are appropriated to the Office of the Assistant Secretary for Health, Department of Health and Human Services, and awarded and administered by the NIH.

Foreign Contracts

The NIH awards contracts for scientific projects directed toward specific areas and research and development needed by the NIH. Contracts with institutions outside the United States must comply with special criteria prescribed for such awards.

AIDS International Training and Research Program

The FIC AIDS International Training and Research Program enables U.S. universities and other research institutions to increase the capacity of developing countries to deal with the AIDS epidemic through training in epidemiological research, clinical trials and other prevention programs, and to build infrastructure for coordinated international testing of candidate HIV/AIDS vaccines and other interventions.

Fogarty International Research Collaboration Award

FIC established the Fogarty International Research Collaboration Award in FY 92 to enable U.S. scientists to cooperate with regions of the world that present new scientific opportunities, including the former Soviet Union, Central and Eastern Europe, Latin America, and the Caribbean. Small research grants are provided to NIH grantees and foreign collaborators for supplies and materials, small equipment, and travel support to conduct cooperative international studies. The program was expanded in FY 95 to include Africa, Asia, the Middle East, and the Pacific Ocean Islands.

HIV/AIDS and Related Illnesses Collaboration Award

FIC provides small research grants for collaboration between NIH grantees and foreign collaborators to conduct research on HIV infection, AIDS, and areas related to AIDS. The main objective is to facilitate unique and highly promising collaborative basic and applied research efforts between U.S. and foreign scientists that will both expand and enhance the HIV- and AIDS-related NIH-supported research program of the U.S. Principal Investigator and benefit the scientific interests of the collaborating foreign scientist.

International Cooperative Biodiversity Groups Program

The International Cooperative Biodiversity Groups (ICBG) Program is an interagency effort cosupported by the NIH (FIC, National Cancer Institute, National Institute of Allergy and Infectious Diseases, National Institute of Mental Health), the U.S. Agency for International Development (USAID), and the National Science Foundation. The ICBG Program was established to identify new therapeutic agents through the analysis of plants and organisms from natural ecosystems and traditional medicines, promote strategies to protect threatened biodiversity, and promote economic growth.

International Training and Research Program in Emerging and Infectious Diseases

In collaboration with the National Institute of Allergy and Infectious Diseases and the National Institute of Dental Research, FIC funds U.S. universities to expand NIH research training efforts in studies of emerging infectious diseases. The long-term objective is to train teams of scientists in regions of the world that provide unique opportunities to understand the fundamental biology, epidemiology, and control of microbial diseases. The Program focuses on research training in the changing patterns of infectious diseases, including genetic evolution, geographical spread, and social factors such as economic development and land use.

International Training and Research Program in Environmental and Occupational Health

In collaboration with the National Institute of Environmental Health Sciences, the National Institute for Occupational Safety and Health, and the Center for Environmental Health of the Centers for Disease Control and Prevention, FIC funds U.S. nonprofit public or private institutions to support international training and research in general environmental and occupational health for scientists and health professionals from developing countries. The goal of the program is to train foreign scientists in epidemiological research, environmental monitoring, engineering control, and prevention research programs.

International Training and Research Program in Population and Health

In cooperation with the National Institute of Child Health and Human Development, FIC funds U.S. nonprofit public or private institutions to support training and research programs in population-related sciences for scientists and health professionals from developing countries. This Program aims to enhance domestic population research programs through training and international collaborative studies related to population, including the study of reproductive processes, contraceptive development, contraceptive and reproductive evaluation, reproductive epidemiology, and social and behavioral factors that influence population dynamics.

Minority International Research Training Grant

In cooperation with the NIH Office of Minority Health, FIC funds the Minority International Research Training Grant Program to provide international training and research opportunities for minorities underrepresented in the scientific professions. Institutional training grants are provided to U.S. colleges and universities to support undergraduate and graduate training at foreign institutions. Awards are also provided to faculty members to conduct independent research abroad and serve as mentors to students abroad.

Special International Programs in Tropical Infectious Diseases and Tuberculosis

The National Institute of Allergy and Infectious Diseases (NIAID) supports four special international programs in tropical infectious diseases and one in tuberculosis.

(1) International Collaboration in Infectious Diseases Research Awards

Under the International Collaboration in Infectious Diseases Research (ICIDR) Program, emphasis is given to developing relationships between U.S. institutions and counterpart institutions abroad in infectious diseases research. The ICIDR Program was begun in 1979, when International Centers for Medicine Research (started in 1962) were phased out.

(2) Tropical Disease Research Unit (TDRU) awards support multidisciplinary centers of research excellence in the United States.

(3) Tropical Medicine Research Center (TMRC) awards are direct funding to outstanding institutions located in the tropics.

(4) The new Tuberculosis and Research Center supports the efforts of investigators at a U.S. university to coordinate a network of domestic and international centers for study of this re-emerging disease.

(5) The NIAID-USAID Middle Eastern Regional Cooperation (MERC) Program began in 1980 to promote cooperation between Israeli and Arab institutions in vector-borne diseases.

HIV Network

In 1987, NIAID launched the International Collaboration in AIDS Research (ICAR) Program, modeled after the ICIDR Program. The ICAR awards were followed by the Preparing for AIDS/HIV Vaccine Evaluation (PAVE) awards, which supported U.S. institutions for a 2-year period to work with developing countries to identify and develop populations in which vaccine and other prevention studies could be conducted. NIAID now supports an International AIDS Vaccine Master Contract, which makes awards to the HIV Network (HIVNET), comprising U.S. institutions and their partners in developing countries.

FELLOWSHIPS AND SCIENTIST EXCHANGES

Foreign Work/Study Assignments

The Foreign Work/Study Program involves overseas work assignments that are developed by NIH professionals not only to meet their own training and experience needs but to contribute to the domestic and international goals of the U.S. Department of Health and Human Services. Potential assignments are developed directly with foreign institutions, U.S. organizations that have overseas installations, or other appropriate organizations that can provide a foreign work/study experience that would fulfill program objectives.

International Neurological Science Fellowships

The International Neurological Science Fellowship Program provides opportunities for junior or mid-career health professionals and scientists in the neurological sciences to enhance their basic or clinical science research skills in a research setting in the United States. The objective of this Program is to prepare candidates for leadership positions in research, academic, and public health institutions in their home countries. The National Institute of Neurological Disorders and Stroke administers the program in collaboration with the World Health Organization.

International Research Fellowships

The FIC International Research Fellowship Program provides awards to foreign scientists in the formative stages of their careers to come to the United States for up to 2 years to receive advanced research experience. Fellows are required to return to their home countries at the termination of their fellowships.

International Visiting Scientists and Technical Exchange Program

The International Visiting Scientists and Technical Exchange (INVEST) Program, National Institute on Drug Abuse (NIDA), promotes international collaboration in drug abuse research among scientists in the United States and worldwide. NIDA's INVEST Program includes research fellowship opportunities (Hubert H. Humphrey Drug Abuse Fellowship and INVEST Research Fellowship), technical consultation and scientific exchange, information dissemination, and international research communications networking.

National Cancer Institute's (NCI) Short-Term Scientist Exchange Program

NCI's Short-Term Scientist Exchange Program, sponsored by the Office of International Affairs, promotes collaborative research between established U.S. and foreign scientists by supporting, in part, exchange visits of U.S. cancer researchers to foreign laboratories, or foreign cancer researchers to U.S. laboratories. The visits may be from 1 week to 6 months in duration.

Career Development Awards for Young Cancer Researchers in the Newly Independent States of the Former USSR

This NCI program makes a limited number of awards to young cancer researchers in these countries, thus allowing them to remain productive during this period of transition to a market economy.

Oncology Research Faculty Development Program

NCI supports the Oncology Research Faculty Development Program for cancer researchers who have a minimum of 3 years of postdoctoral cancer research experience. The program provides advanced research training at NCI laboratories or at U.S. laboratories of NCI grantees for a period of 1 to 3 years. Only candidates from developing countries are eligible.

National Research Service Awards

Under NIH National Research Service Awards, predoctoral, postdoctoral, and special fellowships to promote training for research in health-related sciences are granted each year to U.S. citizens, noncitizen nationals of the United States, or persons who have been lawfully admitted to the United States for permanent residence to pursue training in U.S. institutions. With acceptable justification, these fellowships may be taken at foreign institutions. Fellowships are not awarded for study leading to professional degrees.

Scholars-in-Residence

The FIC Scholars-in-Residence Program enables a small number of eminent U.S. and foreign scientists to come to the NIH each year to interact with the scientific staff and to conduct advanced studies in biomedicine or international health research issues. Scholars are nominated by NIH scientists and spend up to 12 months in residence at the NIH.

Senior International Fellowships

The FIC Senior International Fellowship Program provides opportunities for established U.S. faculty members who have demonstrated productive scholarship and achieved recognized stature in their professions to go abroad to conduct collaborative research and to share their expertise. It is intended that this award be a career-enhancing educational experience with mutual benefits to both home and host institutions.

Visiting Fellows, Associates, and Scientists

The NIH Visiting Program offers talented scientists throughout the world the opportunity to share the research resources of the NIH. Through this Program, scientists at all levels of their careers are invited to the NIH to receive further research training and to conduct research in their biomedical specialties.

International Travel

International travel is defined as travel done by NIH personnel under U.S. Department of Health and Human Services travel orders to locations outside the United States, including Canada and Mexico. This includes travel for contract or grant site visits, under bilateral exchanges to attend international meetings, and to participate in the activities of multilateral organizations, such as the World Health Organization and the Pan American Health Organization.

PROGRAM SUPPORT

Bilateral Exchanges

Bilateral exchanges contribute to the advancement of biomedical and behavioral science for the benefit of health in the United States and also serve such purposes as the following:

- overcoming social or political barriers;
- fostering or sharing of technical resources and expertise;
- drawing on unique resources or settings; and
- furthering U.S. foreign policy objectives.

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